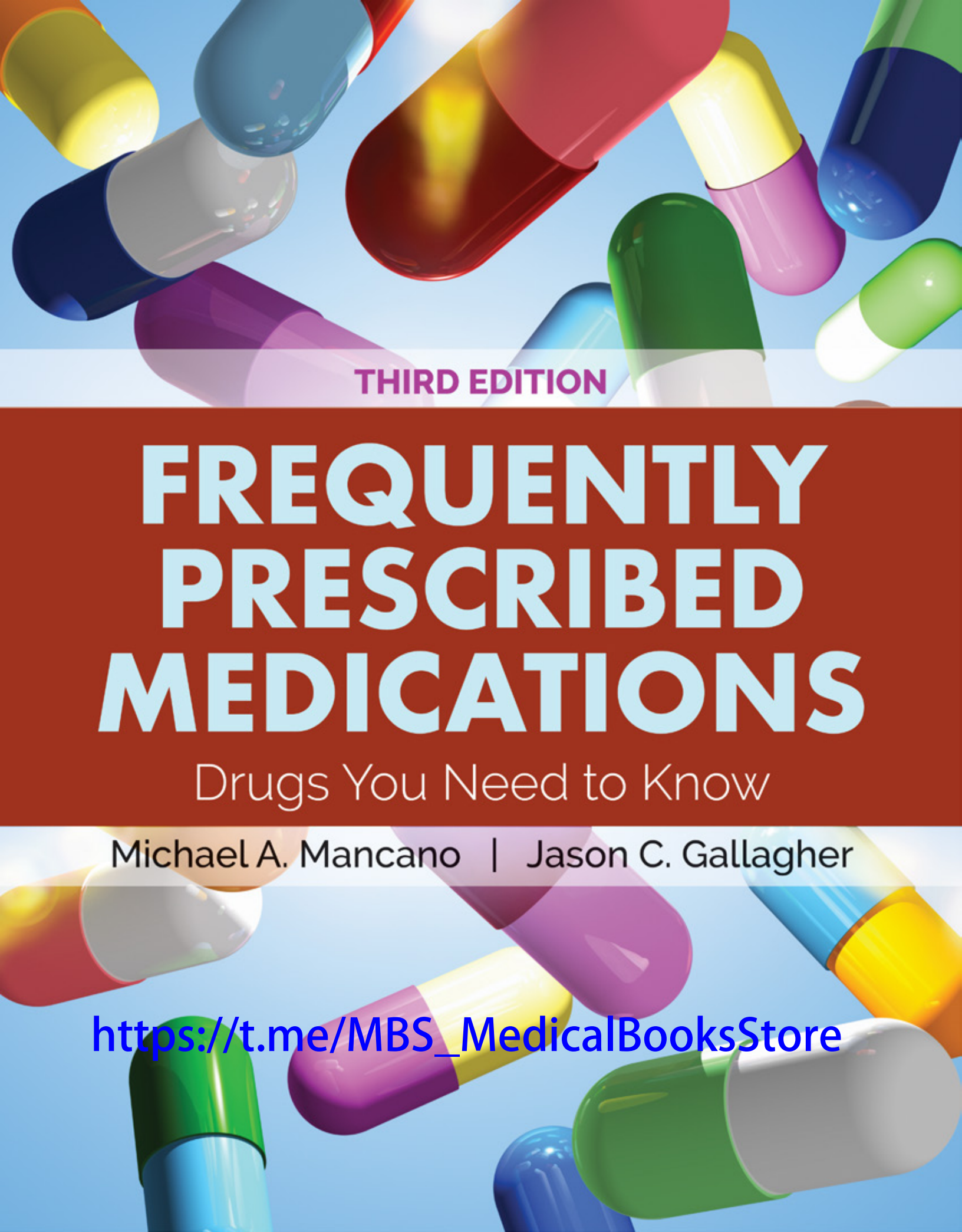

THIRD EDITION

FREQUENTLY PRESCRIBED MEDICATIONS

Drugs You Need to Know

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To the alumni, present students, and future students
of Temple University School of Pharmacy

Brief Contents

Contents

A Message from the Authors

The genesis of this text was as a resource for Temple University School of Pharmacy (TUSP) students to prepare for their "Top 200 Exam," which is an exam about highly pertinent facts for frequently prescribed medications that all students in third professional year must pass before beginning the fourth professional year. Before writing earlier versions of this book, faculty at TUSP reviewed many texts, flash cards, and other resources but found none to be an optimal reference for our students' needs. Many texts were extraordinarily detailed or did not emphasize important information clearly and concisely since drugs were included based on sales or volume instead of factoring importance. For the past 15 years at Temple, we have used annually updated versions of this text, and students and faculty have found them to be very helpful resources. The three published editions of this text expand on the original in-house versions by including review questions and key points for each drug and drug class.

We hope that this text will serve as a useful reference for healthcare students and professionals of various disciplines as they learn the most frequently used medications in clinical practice.

Thank you,

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Preface

The primary goal of this text is not to cover every medication available, but to highlight the most commonly prescribed and utilized medications in the United States. These medications and the central issues with their use are essential knowledge for healthcare students prior to initiating their curricular clinical experiences. Focusing on the most commonly prescribed medications should result in the medications of highest importance being included, but it can also result in some inadvertent exclusions, such as for specialty medications and those that are rising in utility.

New to this Edition

In creating the third edition of the text, we reviewed the current usage patterns of medications available in the United States. In doing so, over 100 new drugs and drug products were added to this edition of the text. Specifically, the "Mechanism of Action" section for each drug class was expanded to include more detail. All aspects of each drug and drug class were updated to include new dosage forms, dosing schedules, side effects, drug interactions, and new indications. A final addition is 30 new review questions that were added at the end of every chapter.

Acknowledgments

Over the last 15 years, numerous revisions of this text have been undertaken. We are indebted to the many clinicians and faculty who have assisted in developing and editing this text over the years. We would like to thank all of the section editors, authors, and the following people. Without their assistance, earlier versions of this text could not have been written. These individuals are (in alphabetical order):

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Abbreviations Used in the Text

5-HT_3 receptors	Serotonin subtype-3 receptors
ACC/AHA	American College of Cardiology/American Heart Association
ACE	Angiotensin converting enzyme
ACE-I	Angiotensin converting enzyme inhibitor
ADHD	Attention deficit hyperactivity disorder
AIDS	Acquired immune deficiency syndrome
ALA	Alpha linoleic acid
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ARB	Angiotensin receptor blocker
ARDS	Acute respiratory distress syndrome
ASCVD	Arthrosclerotic cardiovascular disease
AST	Aspartate aminotransferase
BAS	Bile acid sequestrant
BMT	Bone marrow transplant
BPH	Benign prostatic hyperplasia
BZD	Benzodiazepine
CABG	Coronary artery bypass graft
CBC	Complete blood count
cGMP	Cyclic guanosine monophosphate
CHF	Congestive heart failure
CIN	Contrast-induced nephropathy
CKD	Chronic kidney disease
ClCrest	Estimated creatinine clearance
CNI	Calcineurin inhibitors
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COX-2	Cyclooxygenase-2
CPK	Creatine phosphokinase
CrCl	Creatinine clearance
CRF	Chronic renal failure
CTZ	Chemoreceptor trigger zone
CVA	Cerebrovascular accident
CYP	Cytochrome P450
DHA	Docosahexaenoic acid
DHEA	Dehydroepiandrosterone
DIC	Disseminated intravascular coagulopathy
DKA	Diabetic ketoacidosis
DMARD	Disease modifying antirheumatic drug
DNA	Deoxyribonucleic acid
DRESS	Drug reaction with eosinophilia and systemic symptoms
DVT	Deep vein thrombosis
eGFR	Estimated Glomerular Filtration Rate
EKG	Electrocardiogram
EPA	Eicosapentaenoic acid
EPS	Extrapyramidal symptoms
ER	Extended release
ESRD	End stage renal disease
FAP	Familial adenomatous polyposis
FDA	U.S. Food and Drug Administration
G6PD	Glucose-6-phosphate dehydrogenase
G-CSF	Granulocyte colony-stimulating factor
GERD	Gastroesophageal reflux disease
GFR	Glomerular filtration rate
GI	Gastrointestinal
GU	Genitourinary
HCT	Hematocrit
HCTZ	Hydrochlorothiazide
HDL	High-density lipoprotein
HFrEF	Heart Failure with Reduced Ejection Fraction
HGB	Hemoglobin
HIT	Heparin-induced thrombocytopenia
HIV	Human immunodeficiency virus
HMG-CoA	Hydroxymethylglutaryl-coenzyme A
HPA	Hypothalamic-pituitary-adrenal axis
IBS	Irritable bowel syndrome
IM	Intramuscular
INR	International normalized ratio
IOP	Intraocular pressure
IR	Immediate release
IV	Intravenous
LDL	Low-density lipoprotein
LDLR	Low-density lipoprotein receptors
LFT	Liver function test
LMWH	Low molecular weight heparin
MAO	Monoamine oxidase
MAOI	Monoamine oxidase inhibitor
MDI	Metered-dose inhaler
MI	Myocardial infarction
MOA	Mechanism of action
MRI	Magnetic resonance imaging
MRSA	Methicillin Resistant *Staphylococcus aureus*
NG tube	Nasogastric tube
NLO	Nasolacrimal occlusion
NMS	Neuroleptic malignant syndrome
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NSAID	Nonsteroidal anti-inflammatory drug
NTE	Not to exceed
OAB	Overactive bladder
OTC	Over the counter

PBPC	Peripheral blood progenitor cell collection
PCI	Percutaneous coronary intervention
PCP	*Pneumocystis carinii* pneumonia
PCSK9	Proprotein convertase subtilisin kexin type 9
PDE5	Phosphodiesterase type 5
PE	Pulmonary embolism
PI	Protease inhibitor
PPARα	Peroxisome proliferator activated receptors
PPI	Proton pump inhibitor
PSA	Prostate Specific Antigen
PTCA	Percutaneous transluminal coronary angioplasty
PUD	Peptic ulcer disease
RA	Rheumatoid arthritis
RDA	Recommended dietary allowance
RNA	Ribonucleic acid
SCN	Severe chronic neutropenia
SCr	Serum creatinine
SGLT2	Sodium glucose cotransporter 2
SJS	Stevens-Johnson syndrome
SLE	Systemic lupus erythematosus
SSRI	Selective serotonin-reuptake inhibitor
SUB-Q	Subcutaneous
TCA	Tricyclic antidepressant
TD	Transdermal
TG	Triglyceride
TIA	Transient ischemic attack
TLC	Therapeutic lifestyle changes
TMJ	Temporomandibular joint
TNF	Tumor necrosis factor
TPA	Tissue plasminogen activator
UFH	Unfractionated heparin
VKA	Vitamin K antagonist
VLDL	Very low density lipoprotein

Pregnancy Category Information

All medications covered in this text have pregnancy classification information. However, for some of the medications, the current information is the pregnancy category classes that have been in effect since 1980 (i.e., Category A, B, C, D, X).

You will notice that some medications do not utilize the prior system. In 2015, the FDA replaced the former pregnancy risk letter categories with new information to make them more meaningful to both patients and healthcare providers. The FDA received comments that the old five-letter system left patients and providers ill-informed and resulted in false assumptions about the actual meaning of the letters. The new labeling system allows better patient-specific counseling and informed decision-making for pregnant women seeking medication therapies. While the new labeling improves the old format, it still does not provide a definitive "yes" or "no" answer in most cases. Clinical interpretation is still required on a case-by-case basis.

The Pregnancy and Lactation Labeling Final Rule (PLLR) went into effect on June 30, 2015; however, the timelines for implementing this new information on drug labels is variable. Prescription drugs submitted for FDA approval after June 30, 2015, will use the new format immediately, while labeling for prescription drugs approved on or after June 30, 2001, will be phased in gradually. Medications approved prior to June 29, 2001, are not subject to the PLLR rule; however, the pregnancy letter category must be removed by June 29, 2018.

Pregnancy Categories

Category A: Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.

Category B: Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

Category C: Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal, or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Category D: There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Category X: Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

CHAPTER 1

Analgesics

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ANALGESICS, NARCOTICS

Introduction

Narcotic analgesics are common medications used for moderate and severe pain. They are given by a variety of different routes of administration and are effective for both nociceptive and neuropathic pain symptoms. Narcotics are highly effective analgesics but are controlled substances with a risk of abuse and diversion.

Mechanism of Action for the Drug Class

Act as μ-opioid receptor agonists, altering the perception and response to pain centrally and peripherally. Tramadol and tapentadol also inhibit the reuptake of norepinephrine, which modifies the ascending pain pathway, in addition to being μ-agonists. Buprenorphine is a μ-agonist with weak κ-antagonist activity. Butorphanol and nalbuphine are both partial agonists of μ- and κ-receptors. The variability of receptor affinity and activity produces varying degrees of analgesia among the agents. Fentanyl, hydromorphone, methadone, morphine, and oxycodone are the strongest opiate analgesics discussed in this section.

Contraindications of the Drug Class

Severe respiratory disease or depression, including acute asthma (unless patient is mechanically ventilated); paralytic ileus

Black Box Warnings of the Drug Class

- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely for respiratory depression, especially during initiation or dose escalation.
- Opioids expose patients to the risks of addiction, abuse, and misuse, potentially leading to overdose and death. Assess each patient's risk prior to prescribing; monitor all patients regularly for development of these behaviors or conditions.
- Accidental ingestion of even one dose of an opioid, especially in children, can result in a fatal overdose.
- Prolonged use of opioids during pregnancy can cause neonatal withdrawal syndrome, which may be life-threatening if not recognized and treated according to protocols developed by neonatology experts

Members of the Drug Class

In this section: Buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone, hydrocodone, tramadol, tapentadol
Others: Alfentanil, butorphanol, codeine, levorphanol, meperidine, nalbuphine, opium tincture, oxymorphone, pentazocine, remifentanil, sufentanil

Buprenorphine

Brand Names

Buprenex, Belbuca, Probuphine, Butrans, Subutex

Generic Name

Buprenorphine

Rx Only

Class III controlled substance

Dosage Forms

Injection, transdermal patch, buccal film, subcutaneous implant, sublingual tablet

Usage

Management of pain severe enough to require around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate; opioid dependence; opioid withdrawal in heroin-dependent hospitalized patients

Pregnancy Category C

Dosing

Pediatric:

- Acute pain (moderate to severe): Children 2–12 years: IM, slow IV: 2–6 μg/kg every 4 to 6 hours

Adult:

- Usual dose: 0.15–0.6 mg every 4 to 8 hours as needed
- Acute pain: 0.3 mg IM or IV every 6 to 8 hours as needed

- Chronic pain:
  - Transdermal patch; opioid-naïve: Initial: 5 µg/hour applied once every 7 days; (maximum patch dose of 20 µg/hr applied once every 7 days). Patients receiving daily dose of 30–80 mg of oral morphine equivalent: 10 µg/hour applied once every 7 days.
  - Buccal film: opioid-naïve patients: Initial: 75 µg once daily. Patients who were receiving daily dose of 30–89 mg of oral morphine equivalents: Initial: 150 µg every 12 hours; Patients who were receiving daily dose of 90–160 mg of oral morphine equivalents: Initial: 300 µg every 12 hours.
- Opioid dependence: Sublingual tablets; day 1: 8 mg PO; usual range 12–16 mg/day during induction with a target dose of 16 mg/day for maintenance
- Opiate withdrawal in heroin-dependent hospitalized patients (unlabeled use): IV 0.3–0.9 mg every 6 to 12 hours
- Hepatic impairment:
  - Buccal film, sublingual tablet: Severe impairment (Child-Pugh class C): Reduce starting dose and reduce titration dose by 50%

Adverse Reactions: Most Common

Sedation, hypotension, dizziness, nausea, vomiting, headache, respiratory depression, constipation, application-site rash (patch, implant)

Adverse Reactions: Rare/Severe/Important

Respiratory depression, QTc prolongation, hepatotoxicity, severe allergic reactions

Major Drug Interactions

Drugs Affecting Buprenorphine

- CNS depressants (including alcohol): Increase sedation and dizziness
- CYP3A4 inhibitors and inducers: Alter buprenorphine's metabolism
- Drugs that can potentially cause QTc prolongation: May increase the risk of arrhythmias
- MAO inhibitors: May increase sedation

Contraindications

Transdermal patch: Management of mild, acute, or intermittent pain; management of pain requiring short-term opioid analgesia; management of postoperative pain.

Essential Monitoring Parameters

CNS depression, blood pressure (for hypotension), liver enzymes

Counseling Points

- Avoid excessive alcohol use
- May cause drowsiness and impair your ability to operate machinery
- May cause constipation requiring laxatives
- May cause physical or psychological dependence with prolonged use
- Notify your healthcare provider if pain is unrelieved
- Do not place direct heat (i.e., heating pads) on patch
- Report any allergic reactions
- Never cut the transdermal patches
- Rotate patch sites on arms, chest, and back; apply to hairless, dry area
- Keep any used and unused patches away from children

Key Points

- **Black Box Warnings:**
  - Misuse or abuse by chewing, swallowing, snorting, or injecting buprenorphine extracted from the buccal film or transdermal system will result in the uncontrolled delivery of buprenorphine and pose a significant risk of overdose and death.
  - Concomitant use of benzodiazepines or other CNS depressants, including alcohol and opioids, may result in profound sedation, respiratory depression, coma, and death.
  - Insertion and removal of implant are associated with the risk of implant migration, protrusion, and expulsion. Rare but serious complications including nerve damage and migration resulting in embolism and death may result from improper insertion in the upper arm.
- The combination tablet of buprenorphine and naloxone is preferred over buprenorphine monotherapy for maintenance treatment of opioid dependence. Naloxone is a nonabsorbed opiate antagonist that blocks the effects of buprenorphine if it is snorted or injected, making the combination product an abuse-deterrent.
- Patch doses of 20 µg/hr are associated with increased risk of QT interval prolongation
- Buprenorphine can lower seizure threshold and cause seizures in patients at risk
- Prescribers must be certified through the REMS program to prescribe the tablets and transdermal patch

◉ Fentanyl

Brand Names

Abstral, Actiq, Duragesic, Fentora, Sublimaze, Lazanda, Subsys

Generic Name

Fentanyl

Rx Only

Class II controlled substance

Dosage Forms

Transdermal patch, transdermal device, buccal tablets, buccal lozenge, nasal spray, sublingual spray, sublingual tablets, injection

Usage

- *Injection: Relief of perioperative pain; adjunct to general/regional anesthesia*
- *Transdermal patch: Management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options*
- *Transmucosal lozenge, buccal tablet, nasal spray, sublingual tablet/spray: Management of breakthrough cancer pain in opioid-tolerant patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain*

Pregnancy Category C

Dosing

Pediatric:

- Surgery adjunct to anesthesia: Children ≥ 2 years and Adolescents: IV: 2-3 µg/kg/dose every 1 to 2 hours as needed

Adult:

- Transdermal patch: 25–300 µg/hour every 72 hours, depending on 24-hour morphine equivalent (mg/day)
- IV:
- Adjunct to general anesthesia:
  - Low dose: 1–2 µg/kg, depending on the indication
  - Moderate dose (fentanyl plus a sedative–hypnotic): Initial 2–4 µg/kg
  - Maintenance (bolus or infusion): 25–50 mcg every 15 to 30 minutes or 0.5-2 µg/kg/hour
  - High dose (opioid anesthesia): 4–20 µg/kg bolus then 2–10 µg/kg/hour
- Adjunct to regional anesthesia: 50–100 µg IM or slow IV over 1–2 minutes
- Postoperative recovery: IM, slow IV: 50–100 µg every 1–2 hours as needed
- Postoperative pain: Transdermal device: Apply one device to chest or upper outer arm only
- Breakthrough cancer pain:
  - Lozenge: 200 µg PO (consumed over 15 minutes); re-dose 15 minutes after completion of 1st dose if pain is not relieved; maximum of 1 additional dose can be given per pain episode
  - Buccal film: Initial 200 µg
  - Buccal tablet: Initial 100 µg for all patients unless patient already using Actiq
  - Sublingual tablet: 100 µg
  - Nasal and sublingual spray: Initial 100 µg/dose/spray
- Renal-hepatic impairment:
  - Transdermal patch: mild-to-moderate renal-hepatic impairment: reduce dose by 50%

Adverse Reactions: Most Common

Constipation, nausea, vomiting, sedation, dizziness, xerostomia, pruritus (histamine release), skin rash (transdermal)

Adverse Reactions: Rare/Severe/Important

Hallucinations, hypotension, respiratory, and CNS depression

Major Drug Interactions

Drugs Affecting Fentanyl

- Amphetamines: Increase analgesic effects
- Antipsychotic agents: Enhance hypotensive effects
- CNS depressants (including alcohol): Increase sedation and dizziness
- MAO inhibitors: Serotonin syndrome
- Strong and moderate inhibitors of CYP3A4: Decrease metabolism

Fentanyl's Effect on Other Drugs

- CNS depressants: Additive respiratory and CNS depressant effects

Contraindications

- Transdermal patches: Patients requiring short-term therapy, management of acute or intermittent pain, postoperative or mild pain, and in patients who are not opioid tolerant
- Transmucosal buccal tablets, buccal films, lozenges, sublingual tablets, sublingual spray, nasal spray: Contraindicated in the management of acute or postoperative pain and in patients who are not opioid tolerant

Essential Monitoring Parameters

Respiratory and cardiovascular status, blood pressure, heart rate

Counseling Points

- Wear patch for 72 hours; then replace with a new patch
- Rotate the application sites of the transdermal system to reduce skin irritation
- Takes 12 hours for onset of effect of the transdermal system
- Never cut patches
- Avoid direct heat on patches
- Abrupt discontinuation of fentanyl may result in an abstinence syndrome
- Avoid excessive alcohol use
- May cause drowsiness and impair your ability to operate machinery
- May cause constipation requiring laxatives
- May cause physical or psychological dependence with prolonged use
- Notify your healthcare provider if pain is unrelieved
- A new prescription is required for any refill

Key Points

- **Black Box Warnings:**
  - Use with strong or moderate CYP3A4 inhibitors may result in increased effects and potentially fatal respiratory depression. In addition, discontinuation

of a concomitant CYP3A4 inducer may result in increased fentanyl concentrations. Monitor patients receiving any CYP3A4 inhibitor or inducer.
  - Transmucosal (buccal film–tablet, sublingual spray–tablet, lozenge) and nasal spray: Transmucosal and nasal fentanyl formulations are contraindicated in the management of acute or postoperative pain and in opioid nontolerant patients. Substantial differences exist in the pharmacokinetic profile of fentanyl products. Do not convert patients on a µg-per-µg basis from one fentanyl product to another fentanyl product; the substitution of one fentanyl product for another fentanyl product may result in a fatal overdose. Available only through the TIRF REMS ACCESS program, a restricted distribution program with outpatients, prescribers who prescribe to outpatients, pharmacies (inpatient and outpatient), and distributor-required enrollment.
  - Transdermal device: Available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Ionsys REMS Program. For use only in patients in the hospital. Discontinue treatment before patients leave the hospital. Only the patient should activate Ionsys dosing. Accidental exposure to an intact Ionsys device or to the hydrogel component, especially by children, through contact with skin or contact with mucous membranes, can result in a fatal overdose of fentanyl.
  - Transdermal patch: Transdermal patch is contraindicated for use as an as-needed analgesic, in the management of acute or postoperative pain, or in patients who are opioid nontolerant. Monitor closely for respiratory depression during use, particularly during initiation of therapy or after dose increases. Exposure of application site and surrounding area to direct external heat sources (e.g., heating pads, electric blankets, heat, or tanning lamps, sunbathing, hot tubs) may increase fentanyl absorption and has resulted in fatalities. Patients who experience fever or increase in core body temperature should be monitored closely. Accidental exposure to fentanyl transdermal patch has resulted in fatal overdose in children and adults. Strict adherence to recommended handling and disposal instructions is necessary to prevent accidental exposures.
- Fentanyl has a shorter half-life than other opiates in its class
- Do not wear transdermal patches during MRI
- Fever and heat can increase absorption of fentanyl
- Transmucosal products should only be used for breakthrough for chronic cancer pain
- Do *not* use buccal and transdermal fentanyl in narcotic-naïve patients or for acute and postoperative pain
- Use preservative-free solution for epidural and intrathecal use
- Transmucosal, immediate-release fentanyl products (e.g., sublingual tablets and spray, oral lozenges, buccal tablets and soluble film, nasal spray) are only available through the Transmucosal Immediate-Release Fentanyl (TIRF) REMS ACCESS program

Hydrocodone

Brand Names
Zohydro ER, Hysingla ER

Generic Name
Hydrocodone

Rx Only
Class II controlled substance

Dosage Forms
Extended-release 12-hour capsule, extended-release 24-hour capsule

Usage
Management of pain severe enough to require daily, around-the-clock, opioid, long-term treatment and for which alternative treatment options are inadequate

Pregnancy Category
Adverse events have been observed in some animal reproduction studies. Hydrocodone ER is not recommended for use prior to or during labor and delivery. In humans, birth defects, including some heart defects, have been associated with maternal use of opioids, including hydrocodone, during the first trimester of pregnancy.

Dosing
- Hysingla ER: Initial: 20 mg PO once daily. Dose increases may occur in increments of 10–20 mg every 3–5 days as needed to achieve adequate analgesia
- Zohydro ER: Initial: 10 mg PO every 12 hours. Dose increases may occur in increments of 10 mg every 12 hours every 3–7 days as needed to achieve adequate analgesia
- Renal impairment:
  - Hysingla ER: Moderate, severe, and ESRD: Start with 50% of the initial dose
- Hepatic impairment:
  - Severe impairment: Hysingla ER: Initial: Start with 50% of the initial dose; Zohydro ER: Initial: 10 mg PO every 12 hours

Adverse Reactions: Most Common
Nausea, vomiting, constipation

Adverse Reactions: Rare/Severe/Important

QTc interval prolongation, respiratory depression

Major Drug Interactions

Drugs Affecting Hydrocodone

- Alcohol: Enhanced CNS depressant effect
- CNS depressants: Increase sedation and dizziness
- Strong CYP2D6 inhibitors: Decrease serum concentrations of hydrocodone active metabolites
- CYP3A4 inhibitors and inducers: Alter hydrocodone metabolism
- MAO inhibitors: Enhance adverse–toxic effects

Hydrocodone's Effect on Other Drugs

- CNS depressants: Additive effects
- SSRIs: May cause serotonin syndrome

Essential Monitoring Parameters

Respiratory and mental status, blood pressure

Counseling Points

- Do not chew, break, crush, or melt before swallowing
- Do not take with alcohol or products that have alcohol
- Avoid driving and doing other tasks or actions that call for you to be alert
- Do not stop taking this drug abruptly to prevent withdrawal
- Do not use for fast pain relief or on an as-needed basis

Key Points

- **Black Box Warnings:**
  - Swallow ER capsules or tablets whole; crushing, chewing, or dissolving can cause rapid release and a potentially fatal dose
  - Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of hydrocodone ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosage and durations to the minimum required and follow patients for signs and symptoms of respiratory depression and sedation.
  - Use with all CYP3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitant CYP3A4 inducer may result in increased hydrocodone concentrations. Monitor patients receiving hydrocodone ER and any CYP3A4 inhibitor or inducer.
  - Do not administer hydrocodone ER with alcoholic beverages or ethanol-containing products because of the risk of increased plasma levels and potentially fatal overdose of hydrocodone
- Extended-release formulations are used as abuse deterrents
- Do not use on an as-needed basis, only for chronic, severe pain
- Do not crush or chew extended-release formulations

Hydromorphone

Brand Names

Dilaudid, Exalgo

Generic Name

Hydromorphone

Rx Only

Class II controlled substance

Dosage Forms

Liquid oral, immediate-release tablet, extended-release tablet, injection, suppository

Usage

- *Immediate-release tablet, oral solution, injection: Management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate*
- *Extended-release tablet: Management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate*
- *Suppository: Relief of moderate to severe pain such as that caused by biliary colic, burns, cancer, myocardial infarction, renal colic, surgery, and trauma*

Pregnancy Category

Adverse events have been observed in some animal reproduction studies. Some Dosage Forms are specifically contraindicated for use in obstetric analgesia. When used for pain relief during labor, opioids may temporarily affect the heart rate of the baby. Monitor the neonate for respiratory depression if hydromorphone is used during labor.

Dosing

Pediatric:

- Children weighing < 50 kg and Adolescents weighing < 50 kg:
  - Oral: 0.03–0.08 mg/kg per dose PO every 4 hours as needed
  - IV: 0.015 mg/kg per dose every 3–4 hours as needed
  - Continuous IV infusion: 0.003–0.005 mg/kg/hour (max: 0.2 mg/hour)
- Children weighing ≥ 50 kg and Adolescents weighing ≥ 50 kg:
  - Oral: 1–4 mg/dose PO every 3 to 4 hours as needed

- IV: 0.2–0.6 mg/dose every 2 to 4 hours as needed
- IM, SubQ: 0.8–2 mg every 4 to 6 hours as needed
- Rectal: 3 mg every 4 to 8 hours as needed

Adult: Initial:

- Oral: 2–4 mg PO every 4 hours as needed
- IV: 0.2–1 mg every 2 to 4 hours as needed
- IM, SUB Q: 1–2 mg every 2 to 3 hours as needed
- Epidural: 0.4–1 mg bolus; infusion rate: 0.03–0.3 mg/hour

Adult: Maintenance:

- Oral: 2–8 mg PO every 3 to 4 hours as needed
- IV continuous infusion: 0.5–3 mg/hour
- Rectal: 3 mg (1 suppository) every 6 to 8 hours as needed
- Extended-release: 8–64 mg PO every 24 hours in opioid-tolerant patients only
- Renal impairment:
  - Injectable, oral (immediate-release): Initiate with 25–50% of the usual starting dose, depending on the degree of impairment
  - Oral (extended-release tablet): CrCl 40–60 ml/minute: Initiate with 50% of the usual starting dose; CrCl < 30 ml/minute: Initiate with 25% of the usual starting dose
- Hepatic impairment:
  - Injectable, oral (immediate-release): Mild to severe impairment: Initiate with 25–50% of the usual starting dose
  - Oral (extended-release tablet): Moderate impairment: Initiate with 25% of the usual starting dose; Severe impairment: Avoid use

Adverse Reactions: Most Common

Constipation, nausea, vomiting, sedation, dizziness, xerostomia, pruritus

Adverse Reactions: Rare/Severe/Important

Hallucinations, agitation, respiratory, and CNS depression

Major Drug Interactions

Drugs Affecting Hydromorphone

CNS depressants: Increase sedation and dizziness

Hydromorphone's Effect on Other Drugs

- CNS depressants: Additive effects
- MAO inhibitors, SSRIs: Serotonin syndrome

Contraindications

- Hydromorphone ER tablets: Opioid-nontolerant patients; preexisting GI surgery and/or diseases resulting in narrowing of GI tract or blind loops in the GI tract
- Suppository: Intracranial lesion associated with increased intracranial pressure; whenever ventilatory function is depressed

Essential Monitoring Parameters

Respiratory and mental status, blood pressure

Counseling Points

- May cause drowsiness and impair your ability to operate machinery
- May cause constipation, requiring laxatives
- Avoid alcohol use
- May cause physical or psychological dependence with prolonged use
- Notify your healthcare provider if pain is unrelieved
- The extended-release tablets must be swallowed whole
- A new prescription is required for any refill

Key Points

- **Black Box Warnings:**
  - Swallow ER tablets whole; crushing, chewing, or dissolving can cause rapid release and a potentially fatal dose
  - Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of hydromorphone and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosage and durations to the minimum required and follow patients for signs and symptoms of respiratory depression and sedation.
  - Ensure accuracy when prescribing, dispensing, and administering hydromorphone oral solution. Dosing errors due to confusion between mg and ml can result in accidental overdose and death.
  - High-potency hydromorphone (10 mg/ml) is a more concentrated solution of hydromorphone than hydromorphone 1, 2, or 4 mg/ml and is for use in opioid-tolerant patients only. Do not confuse high-potency hydromorphone with standard parenteral formulations of hydromorphone or other opioids, as overdose and death could result.
- Very soluble in injectable form; useful for continuous pump and epidural or intrathecal administration
- Use only preservative-free solution for the epidural and intrathecal route
- All prescribers of Exalgo, extended-release hydromorphone, must be registered in the REMS program and an FDA-approved patient medication guide must be given every time it is dispensed

Methadone

Brand Names

Methadose, Dolophine

Generic Name

Methadone

Rx Only

Class II controlled substance

Dosage Forms

Tablet, soluble tablet, injection, oral solution

Usage

- *Injection: Management of pain severe enough to require an opioid analgesic and for which alternative treatment options are inadequate*
- *Oral (Dolophine only): Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate*
- *Detoxification for opiate addiction (as part of a program)*

Pregnancy Category C

Dosing

- Severe pain:
  - Initial dose:
    - Oral: 2.5 mg PO every 8 to 12 hours
    - IV: 2.5–10 mg PO every 8 to 12 hours
  - Maintenance dose: 15–60 mg PO daily in divided doses
  - Maximum dose: No maximum dose; titrate to response; no ceiling effect
- Addiction:
  - Initial dose: 20–30 mg PO single daily dose
  - Maintenance: 80–120 mg PO single daily dose
- Renal impairment:
  - CrCl < 10 ml/min, reduce dose 50–75%
- Hepatic impairment:
  - Avoid in severe hepatic dysfunction

Adverse Reactions: Most Common

Constipation, nausea, vomiting, sedation, dizziness, xerostomia, pruritus (histamine release)

Adverse Reactions: Rare/Severe/Important

Hallucinations, hypotension, respiratory and CNS depression, ECG changes; QT-interval prolongation

Major Drug Interactions

Drugs Affecting Methadone

- CNS depressants: Increase sedation and dizziness
- Nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs): Reduce methadone levels
- CYP3A4 inducers: Reduce methadone levels
- CYP3A4 inhibitors: Increase methadone levels
- St. John's wort: Decreases methadone levels
- Grapefruit juice: Decreases absorption

Methadone's Effect on Other Drugs

- CNS depressants: Additive respiratory and CNS depressant effects
- QTc-prolonging agents: Additive risk of ventricular arrhythmias
- Stavudine and didanosine: Decrease bioavailability

Contraindications

Concurrent use of selegiline, short-term–acute–postoperative pain

Essential Monitoring Parameters

- Vital signs, mental status, constipation, nausea, pruritus, respiratory depression, and sedation
- Evaluate baseline QTc interval prior to therapy in patients with risk factors for QTc interval prolongation, prior ECG with a QTc > 450 msec, or a history suggesting prior ventricular arrhythmia; Repeat ECG 2 to 4 weeks after initiating therapy and after significant dose increases

Counseling Points

- Abrupt discontinuation of methadone may result in an abstinence syndrome
- Avoid excessive alcohol use
- May cause drowsiness and impair your ability to operate machinery
- May cause constipation, requiring laxatives
- May cause physical or psychological dependence with prolonged use
- Notify your healthcare provider if pain is unrelieved
- A new prescription is required for any refill

Key Points

- **Black Box Warnings:**
  - QTc interval prolongation and serious arrhythmias (e.g., torsades de pointes) have occurred during treatment. Closely monitor patients during initiation and titration for changes in cardiac rhythm.
  - When used for treatment of opioid addiction (detoxification or maintenance), may only be dispensed by certified opioid treatment programs
  - Soluble tablets (diskets): For oral administration only
- When converting patients to methadone from another narcotic, use a calculated equivalent dose, which is dependent on the daily equivalent dose of morphine
- Accumulation can occur with extended use because of the long half-life
- Monitor for sedation with extended use
- Discontinue slowly after prolonged use
- It is unlawful to dispense methadone for addiction maintenance without a license
- Methadone administration for opioid addiction is permitted during inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction, to facilitate the treatment of the primary admitting diagnosis

Morphine

Brand Names

Kadian, MS Contin, Oramorph SR, Roxanol, various others

Generic Name

Morphine

Rx Only

Class II controlled substance

Dosage Forms

Immediate- and sustained-release tablets, injection, oral solution, suppository, intramuscular device

Usage

- *Injection: Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate*
- *Oral: Extended-release: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate; Immediate-release: Management of acute and chronic pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Oral solution 100 mg per 5 ml (20 mg/ml) is for opioid-tolerant patients.*

Pregnancy Category

- Adverse events have been observed in some animal reproduction studies. The frequency of congenital malformations has not been reported to be greater than expected in children from mothers treated with morphine during pregnancy. However, following in utero exposure, infants may exhibit withdrawal, decreased brain volume (reversible), small-size, decreased ventilatory response to CO_2 and increased risk of sudden infant death syndrome.
- Morphine sulfate injection may be used for the management of pain during labor; however, some manufacturers specifically contraindicate use of the injection during labor when a premature birth is anticipated. When used for pain relief during labor, opioids may temporarily affect the heart rate of the baby. Morphine injection may also be used to treat pain following delivery.

Dosing

Pediatric:

- Oral:
  - Weight < 50 kg: 0.2–0.5 mg/kg/dose PO every 3 to 4 hours as needed
  - Weight ≥ 50 kg: 15–20 mg PO every 3 to 4 hours as needed
- IM, IV, or SubQ intermittent
  - Weight < 50 kg: 0.05–0.2 mg/kg/dose every 2 to 4 hours as needed; Infants: 2 mg/dose; Children 1 to 6 years: 4 mg/dose; Children 7 to 12 years: 8 mg/dose; Adolescents: 10 mg/dose
  - Weight ≥ 50 kg: 2–8 mg every 2 to 4 hours as needed
- Continuous IV/SubQ infusion:
  - Weight < 50 kg: 0.01–0.04 mg/kg/hour
  - Weight ≥ 50 kg: 1.5 mg/hour

Adult: Initial:

- Oral:
  - Immediate release: 10–30 mg PO every 4 hours as needed
  - Controlled release: 15–30 mg PO every 12 hours (opioid naive)
- SUB-Q, *IV,* IM: 2.5 mg–10 mg every 2 to 4 hours as needed
- IV, SUB-Q continuous: Opioid tolerant: 0.8–10 mg/hour mg/hour; Epidural: 0.2–0.4 mg/hour

Adult: Maintenance:

- Oral controlled-release: Usual range 60–200 mg/day in divided doses
- IV, SUB-Q, IM: 5–15 mg every 4 hours as needed
- IV, SUB-Q continuous range: 0.5–10 mg/hour up to 80 mg/hour
- Rectal: 10–20 mg every 4 hours

Adult: Maximum:

- Oral, IV, SUB-Q: No maximum dose; titrate to response
- Epidural: 10 mg/24 hours

Adverse Reactions: Most Common

Constipation, nausea, vomiting, sedation, dizziness, xerostomia, pruritus (histamine release)

Adverse Reactions: Rare/Severe/Important

Hallucinations, hypotension, respiratory, and CNS depression

Major Drug Interactions

Drugs Affecting Morphine

- CNS depressants increase sedation and dizziness
- P-glycoprotein–ABCB1 Inducers–Inhibitors may alter morphine's metabolism

Morphine's Effect on Other Drugs

- CNS depressants: Additive effect
- MAO inhibitors: May cause serotonin syndrome
- SSRIs: May cause serotonin syndrome

Contraindications

- Epidural–intrathecal: Astramorph–PF, Duramorph, Infumorph: Infection at infusion site; concomitant anticoagulant therapy; uncontrolled bleeding diathesis; presence of any other concomitant therapy or medical condition that would render administration hazardous; upper airway obstruction.
- Rectal: Severe CNS depression; cardiac arrhythmias, heart failure due to chronic lung disease; increased intracranial or cerebrospinal pressure, head injuries, brain tumor; acute alcoholism, delirium tremens; seizure disorder; use after biliary tract surgery, suspected surgical abdomen, surgical anastomosis.
- MAO inhibitor use (concurrent or within 14 days)

Essential Monitoring Parameters

Respiratory and mental status, blood pressure

Counseling Points

- May cause drowsiness and impair your ability to operate machinery
- May cause constipation, requiring laxatives
- Avoid alcohol use
- May cause physical or psychological dependence with prolonged use
- After prolonged use, abrupt discontinuation of morphine may result in an abstinence syndrome
- Do not crush or chew the controlled-release products
- Notify your healthcare provider if pain is unrelieved
- A new prescription is required for any refill

Key Points

- **Black Box Warnings:**
  - Swallow morphine ER formulations whole (or may sprinkle the contents of the capsule on applesauce and swallow without chewing); crushing, chewing, or dissolving the ER formulations can cause rapid release and absorption of a potentially fatal dose of morphine
  - Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of morphine and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosage and durations to the minimum required and follow patients for signs and symptoms of respiratory depression and sedation.
  - Patients should not consume alcoholic beverages or medication containing ethanol while taking ER capsules; ethanol may increase morphine plasma levels, resulting in a potentially fatal overdose
  - Because of the risk of severe adverse effects when the epidural or intrathecal route of administration is employed, patients must be observed in a fully equipped and staffed environment for at least 24 hours after the initial dose. Single-dose Duramorph neuraxial administration may result in acute or delayed respiratory depression for up to 24 hours. Monitor patients receiving Infumorph for the first several days after catheter implantation.
  - Ensure accuracy when prescribing, dispensing, and administering morphine oral solution
  - Dosing errors due to confusion between mg and ml and other morphine solutions of different concentrations can result in accidental overdose and death
  - Because of the delay in maximum CNS effect with IV administration (30 minutes), rapid IV administration may result in overdosing. Observe patients in a fully equipped and staffed environment for at least 24 hours after each test dose of Infumorph and, as indicated, for the first several days after surgery.
  - Avoid in patients with increase in intracranial pressure, such as with head trauma
  - The equivalent oral dose is three times more than the IV dose
  - Controlled-release products should not be used to treat acute postoperative pain
  - Use preservative-free solutions for epidural and intrathecal use

Oxycodone

Brand Names

Oxaydo, OxyContin, OxyIR, Roxicodone, Xtampza ER

Generic Name

Oxycodone

Rx Only

Class II controlled substance

Dosage Forms

Capsule, oral liquid, oral concentrate, immediate- and controlled-release tablets

Usage

- *Immediate-release formulations: Management of acute or chronic moderate to severe pain where the use of an opioid analgesic is appropriate*
- *Extended-release formulations: Capsules: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in adults; Tablets: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in adults and opioid-tolerant pediatric patients ≥ 11 years of age who are already receiving and tolerating a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent*

Pregnancy Category

Adverse events have been observed in some animal reproduction studies. Oxycodone should not be used immediately prior to or during labor.

Dosing

Pediatric (6 to 12 years):

- Initial dose: 0.1–0.2 mg/kg/dose (moderate pain) or 0.2 mg/kg/dose (severe pain); for severe chronic pain, administer on a regularly scheduled basis, every 4 to 6 hours

Adult:

- Initial:
  - 5–15 mg PO every 4 to 6 hours as needed
  - 10 mg extended-release tablet: Every 12 hours (opioid naive)
  - 9 mg extended-release capsule: Every 12 hours (opioid naive)

- Maintenance extended-release dose: 20–160 mg PO every 12 hours
- Maximum dose: No maximum dose; titrate to response

- Hepatic impairment:
  - Immediate release (adults): Initiate therapy at 33 to 50% of the usual dosage
  - Extended-release tablets (children ≥ 11 years, adolescents, and adults) or extended-release capsules (adults): Initial: Initiate oxycodone ER with 33 to 50% of the calculated recommended dose.

Adverse Reactions: Most Common

Constipation, nausea, vomiting, sedation, dizziness, xerostomia, pruritus (histamine release)

Adverse Reactions: Rare/Severe/Important

Hallucinations, hypotension, respiratory and CNS depression

Major Drug Interactions

Drugs Affecting Oxycodone

- CNS depressants: Increase sedation and dizziness
- CYP3A4 Inhibitors–Inducers: Alteration of oxycodone's metabolism

Oxycodone's Effect on Other Drugs

- CNS depressants: Additive effect
- MAO inhibitors: May cause serotonin syndrome
- SSRIs: May cause serotonin syndrome

Essential Monitoring Parameters

Respiratory and mental status; blood pressure

Counseling Points

- May cause drowsiness and impair your ability to operate machinery
- May cause constipation requiring laxatives
- Avoid alcohol use
- May cause physical or psychological dependence with prolonged use
- After prolonged use, abrupt discontinuation of oxycodone may result in an abstinence syndrome
- Do not crush or chew the controlled-release products
- Notify your healthcare provider if pain is unrelieved
- A new prescription is required for any refill

Key Points

- **Black Box Warnings:**
  - Swallow ER tablets whole; crushing, chewing, or dissolving can cause rapid release and a potentially fatal dose
  - Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of oxycodone and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosage and duration to the minimum required and follow patients for signs and symptoms of respiratory depression and sedation.
  - Use with all CYP3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitant CYP3A4 inducer may result in increased oxycodone concentrations. Monitor patients receiving oxycodone and any CYP3A4 inhibitor or inducer.
  - Ensure accuracy when prescribing, dispensing, and administering oxycodone oral solution.
  - Dosing errors due to confusion between mg and ml and other oxycodone oral solutions of different concentrations can result in accidental overdose
- Commonly found in combination products with acetaminophen and ibuprofen
- Only available in oral formulations
- Controlled-release products should not be used to treat acute postoperative pain
- Deaths due to overdose have been reported due to misuse–abuse after crushing the sustained-release tablets

Tapentadol

Brand Names

Nucynta, Nucynta ER

Generic Name

Tapentadol

Rx Only

Class II controlled substance

Dosage Forms

Immediate- and extended-release tablet

Usage

- *Immediate release: Management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate in adults*
- *Extended release: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate;* neuropathic pain associated with diabetic peripheral neuropathy

Pregnancy Category C

Dosing

- Acute pain: Initial: 50–100 mg PO every 4 to 6 hours as needed; maximum daily dose on day 1 of 700 mg/day and 600 mg/day on subsequent days
- Chronic pain: Extended-release: Initial: 50 mg PO every 12 hours, may titrate every 3 days (therapeutic range: 100–250 mg every 12 hours)
- Neuropathic pain associated with diabetic peripheral neuropathy: Extended-release: Initial: 50 mg

PO every 12 hours (therapeutic range: 100 to 250 mg every 12 hours)
- Renal impairment:
  - CrCl < 30 ml/minute: Use not recommended
- Hepatic impairment:
  - Moderate impairment (Child-Pugh class B): Immediate release: Initial: 50 mg PO every 8 hours or longer (maximum: 150 mg/24 hours); Extended release: Initial: 50 mg PO every 24 hours or longer; maximum: 100 mg/day
  - Severe impairment (Child-Pugh class C): Use not recommended

Adverse Reactions: Most Common

Sedation, hypotension, dizziness, nausea, vomiting, constipation, pruritus

Adverse Reactions: Rare/Severe/Important

Serotonin syndrome, seizure, respiratory depression

Major Drug Interactions

Drugs Affecting Tapentadol

- Alcohol may enhance the CNS depressant effect and increase absorption of extended-release product
- CNS depressants may increase the sedation
- MAO inhibitors, TCAs, and SSRIs may increase the risk of seizures and serotonin syndrome
- Naloxone may induce a seizure

Tapentadol's Effect on Other Drugs

CNS depressants: Additive respiratory and CNS depressant effects

Contraindications

Use of MAO inhibitors within 14 days

Essential Monitoring Parameters

Respiratory and cardiovascular status, blood pressure, heart rate

Counseling Points

- May cause drowsiness and impair your ability to operate machinery
- May cause constipation requiring laxatives
- Avoid alcohol use
- May cause physical or psychological dependence with prolonged use
- After prolonged use, abrupt discontinuation may result in an abstinence syndrome
- Do not crush or chew the extended-release products
- Notify your healthcare provider if pain is unrelieved
- A new prescription is required for any refill

Key Points

- **Black Box Warnings:**
  - Swallow ER tablets whole; crushing, chewing, or dissolving can cause rapid release and a potentially fatal dose
  - Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of tapentadol and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosage and durations to the minimum required and follow patients for signs and symptoms of respiratory depression and sedation.
  - Patients should not consume alcohol or medication containing ethanol while taking tapentadol ER; ethanol may increase tapentadol plasma levels, resulting in a potentially fatal overdose
- Only available in oral formulations
- Extended-release products are not intended for the management of acute or postoperative pain
- An FDA-approved patient medication guide must be given every time it is dispensed
- May be confused with tramadol
- Use caution in patients with a seizure history

Tramadol

Brand Names

ConZip, Ultram, Ultracet

Generic Name

Tramadol

Rx Only

Class IV controlled substance

Dosage Forms

Immediate-release tablet, extended-release tablet; Ultracet is a combination with acetaminophen

Usage

Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate; restless leg syndrome

Pregnancy Category C

Dosing

- Immediate Release: 50–100mg PO every 4 to 6 hours as needed (maximum: 400 mg/day)
- Extended Release: 100 mg PO once daily (maximum: 300 mg/day) Renal impairment:
  - Immediate Release: CrCl < 30 ml/minute: Increase dosing interval to every 12 hours (maximum: 200 mg/day); Dialysis: Increase dosing interval to every 12 hours; (maximum: 200 mg/day)
  - Extended Release: CrCl < 30 ml/minute: Avoid use.
- Hepatic impairment:
  - Immediate release: Cirrhosis: 50 mg every 12 hours
  - Extended release: Severe impairment (Child-Pugh class C): Avoid use

Adverse Reactions: Most Common

Sedation, dizziness, constipation, nausea and vomiting, somnolence, euphoria–dysphoria

Adverse Reactions: Rare/Severe/Important

Hypotension, seizures at ≥ 500 mg/day (discontinuation)

Major Drug Interactions

Drugs Affecting Tramadol

- Carbamazepine: Decreases tramadol levels
- CYP2D6 and CYP3A4 Inhibitors: Alteration of tramadol's metabolism
- MAO inhibitors, TCAs, and SSRIs: May increase the risk of seizures and serotonin syndrome
- Naloxone: May induce a seizure

Tramadol's Effect on Other Drugs

CNS depressants: Additive respiratory and CNS depressant effects

Contraindications

Concomitant use with or within 14 days following MAO inhibitor therapy

Essential Monitoring Parameters

Respiratory rate, blood pressure, and pulse

Counseling Points

- Extended-release tablets must be swallowed whole
- May cause drowsiness
- Abrupt discontinuation may result in withdrawal symptoms

Key Points

- **Black Box Warnings:**
  - Swallow ER tablets whole; crushing, chewing, or dissolving can cause rapid release and a potentially fatal dose
  - Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of tramadol and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosage and durations to the minimum required and follow patients for signs and symptoms of respiratory depression and sedation.
  - The effects of concomitant use or discontinuation of CYP3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol are complex. Use of CYP3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1.
- Serotonin syndrome or seizures can occur when combined with antidepressants
- Use with caution in patients with a seizure history
- Tramadol was recategorized as a controlled substance in 2014 by the US DEA after it was determined that it has abuse potential. Older references may reference tramadol as noncontrolled.
- May be confused with tapentadol, Toradol, or trazodone

NARCOTIC/NON-NARCOTIC COMBINATIONS

Introduction

Narcotic combinations are common agents prescribed for management of moderate pain. The nonnarcotic agents used are most commonly ibuprofen or acetaminophen, which work as a co-analgesic. The side effects of the individual components must be considered. These drugs are classified as controlled substances and have the risk of abuse and diversion.

Mechanism of Action for the Drug Class

The narcotic component binds to opioid μ-receptors, altering the perception and response to pain. The nonnarcotic analgesics have mechanisms of action that vary by agent. See their individual sections for details.

Contraindications of the Drug Class

Significant respiratory depression (in unmonitored settings), acute or severe bronchial asthma, hypercapnia, paralytic ileus

Black Box Warnings for the Drug Class

- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely for respiratory depression, especially during initiation or dose escalation.
- Opioids expose patients and other users to the risks of addiction, abuse, and misuse, potentially leading to overdose and death. Assess each patient's risk prior to prescribing; monitor all patients regularly for development of these behaviors or conditions.

- Accidental ingestion of even one dose of an opioid, especially in children, can result in a fatal overdose.
- Prolonged use of opioids during pregnancy can cause neonatal withdrawal syndrome, which may be life-threatening if not recognized and treated according to protocols developed by neonatology experts.

Members of the Drug Class

In this section: Codeine–acetaminophen, hydrocodone–acetaminophen, hydrocodone–ibuprofen, and oxycodone–acetaminophen;
Others: Pseudoephedrine–hydrocodone–chlorpheniramine

◉ Codeine–Acetaminophen

Brand Names

Capital and Codeine, Tylenol 2, Tylenol 3, Tylenol 4, Tylenol with Codeine

Generic Name

Codeine–acetaminophen

Rx Only

Tablets: Class III controlled substance Solution: Class V controlled substance

Dosage Forms

Tablet, oral solution–suspension

Usage

Management of mild to moderate pain where treatment with an opioid is appropriate and for which alternative treatments are inadequate

Pregnancy Category C

Dosing

Pediatric (solution/suspension):

- 3 to 6 years: 5 ml PO 3 to 4 times daily as needed
- 7 to 12 years: 10 ml PO 3 to 4 times daily as needed

Adult:

- Solution–suspension: 15 ml PO every 4 hours as needed
- Tablets: Acetaminophen (300–1000 mg/dose)–codeine (15–60 mg/dose) PO every 4 hours as needed
- Maximum dose: 360 mg of codeine component/day; 3000 mg of acetaminophen component/day
- Hepatic impairment:
  - Use with caution. Limited, low-dose therapy acetaminophen is usually well tolerated in hepatic disease–cirrhosis. However, cases of hepatotoxicity at daily acetaminophen dosages < 4 g daily have been reported.

Adverse Reactions: Most Common

Constipation, nausea, vomiting, sedation, dizziness, xerostomia, pruritus

Adverse Reactions: Rare–Severe–Important

Hallucinations, hypotension, respiratory and CNS depression, hepatotoxicity (exceeding acetaminophen dosing recommendations)

Major Drug Interactions

Drugs Affecting Codeine–Acetaminophen

- CYP2D6 inhibitors: Prevent conversion of codeine to its active metabolite morphine
- CNS depressants: Increase sedation and dizziness
- Ethanol use: > 3 drinks/day may increase risk of hepatotoxicity
- Isoniazid: May increase the risk hepatotoxicity

Codeine–Acetaminophen's Effect on Other Drugs

- Warfarin: Increased anticoagulant effect
- CNS depressants: Additive effects

Contraindications

Postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy; concurrent use with monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days.

Essential Monitoring Parameters

Respiratory and mental status, blood pressure, heart rate

Counseling Points

- May cause drowsiness and impair your ability to operate machinery
- May cause constipation, requiring laxatives
- Avoid alcohol use
- May cause physical or psychological dependence with prolonged use
- After prolonged use, abrupt discontinuation may result in an abstinence syndrome
- Notify your healthcare provider if pain is unrelieved

Key Points

- **Black Box Warnings:**
  - Acetaminophen has been associated with cases of acute liver failure, at times, resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at dosages that exceed 4 g/day and often involve more than one acetaminophen-containing product.
  - Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of acetaminophen–codeine and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.
  - The concomitant use of codeine with all CYP3A4 inhibitors or discontinuation of a CYP3A4 inducer

may result in an increase in codeine plasma concentrations with subsequently greater metabolism by CYP450 2D6, resulting in greater morphine levels, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. The concomitant use of codeine with all CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor may result in lower codeine levels, greater norcodeine levels, and less metabolism via 2D6 with resultant lower morphine levels. The concomitant use of codeine with all CYP450 2D6 inhibitors may result in an increase in codeine plasma concentrations and a decrease in the plasma concentration of the active metabolite, morphine. The discontinuation of a CYP450 2D6 inhibitor may result in a decrease in codeine plasma concentrations and an increase in the plasma concentration of the active metabolite, morphine. Follow patients receiving acetaminophen–codeine and any CYP2D6 inhibitor or CYP3A4 inhibitor or inducer for signs and symptoms that may reflect opioid toxicity and opioid withdrawal when acetaminophen–codeine are used in conjunction with inhibitors of CYP2D6 or inhibitors and inducers of CYP3A4.
    - Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and were found to have evidence of being ultrarapid metabolizers of codeine due to a CYP2D6 polymorphism
    - Dosing errors due to confusion between mg and ml and other acetaminophen–codeine oral suspensions of different concentrations can result in accidental overdose and death. Ensure accuracy when prescribing, dispensing, and administering oral suspension.
- Differences in individual metabolism means that some patients will not convert codeine to its active form, necessitating the use of other agents; others may be ultrarapid metabolizers of codeine, producing higher levels of morphine and leading to more numerous or intense adverse effects
- Caution during breastfeeding; use lowest possible effective dose
- Controlled substance
- Do not exceed acetaminophen daily dosing recommendations

◉ Hydrocodone–Acetaminophen

Brand Names

Lorcet, Lortab, Norco Vicodin, various others

Generic Name

Hydrocodone–acetaminophen

Rx Only

Class II controlled substance

Dosage Forms

Tablet, capsule, oral solution, elixir

Usage

Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate

Pregnancy Category C

Dosing

Pediatric:

- Children ≥ 2 years and Adolescents < 50 kg: 0.1–0.2 mg/kg per dose hydrocodone component every 4 to 6 hours; ≥ 2 years and adolescents ≥ 50 kg: Initial: 5–10 mg hydrocodone component every 4 to 6 hours

Adult:

- Usual dose: 2.5–10 mg hydrocodone component PO every 4 to 6 hours
- Maximum dose: 3000 mg of acetaminophen component PO/day
- Hepatic impairment:
    - Use with caution. Limited, low-dose therapy acetaminophen is usually well tolerated in hepatic disease–cirrhosis. However, cases of hepatotoxicity at daily acetaminophen dosages < 4 g daily have been reported.

Adverse Reactions: Most Common

Constipation, nausea, vomiting, sedation, dizziness, xerostomia, pruritus (histamine release)

Adverse Reactions: Rare/Severe/Important

Hallucinations, hypotension, respiratory and CNS depression, hepatotoxicity (exceeding acetaminophen dosing recommendations)

Major Drug Interactions

Drugs Affecting Hydrocodone–Acetaminophen

- CNS depressants: Increase sedation and dizziness
- CYP3A4 Inhibitors and Inducers: Alteration of hydrocodone's metabolism
- Ethanol use: > 3 drinks/day may increase risk of hepatotoxicity
- Isoniazid: May increase the risk of hepatotoxicity

Hydrocodone–Acetaminophen's Effect on Other Drugs

- Warfarin: Increases anticoagulant effect
- CNS depressants: Additive effect

Essential Monitoring Parameters

Respiratory and mental status, blood pressure

Counseling Points

- May cause drowsiness and impair your ability to operate machinery
- May cause constipation, requiring laxatives
- Avoid alcohol use

- May cause physical or psychological dependence with prolonged use
- After prolonged use, abrupt discontinuation may result in an abstinence syndrome
- Notify your healthcare provider if pain is unrelieved

Key Points

- **Black Box Warnings:**
  - Acetaminophen has been associated with cases of acute liver failure, at times, resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed > 4 g/day; and often involve more than one acetaminophen-containing product.
  - Use with all CYP3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitant CYP3A4 inducer may result in increased hydrocodone concentrations. Monitor patients receiving hydrocodone–acetaminophen and any CYP3A4 inhibitor or inducer.
- Schedule III controlled substance
- Do not exceed acetaminophen daily dosing recommendations

◉ Hydrocodone–Ibuprofen

Brand Names

Ibudone, Reprexain, Vicoprofen

Generic Name

Hydrocodone–ibuprofen

Rx Only

Class II controlled substance

Dosage Form

Tablet

Usage

Short-term (generally < 10 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate

Pregnancy Category

Adverse events have been observed in some animal reproduction with this combination. In humans, birth defects, including some heart defects, have been associated with maternal use of opioid analgesics, including hydrocodone, during the first trimester of pregnancy. Because they may cause premature closure of the ductus arteriosus, the use of NSAIDs late in pregnancy should be avoided.

Dosing

- Usual adult dose: 1 tablet (hydrocodone 2.5 mg–10 mg/ibuprofen 200 mg) every 4 to 6 hours
- Maximum dose: 5 tablets per day
- Renal impairment:
  - Avoid use in advanced renal disease
- Hepatic impairment:
  - Use with caution; initiate therapy with a low dose and monitor closely in severe impairment

Adverse Reactions: Most Common

Constipation, nausea, vomiting, sedation, dizziness, xerostomia, pruritus (histamine release), dyspepsia

Adverse Reactions: Rare/Severe/Important

Hallucinations, hypotension, respiratory and CNS depression, edema, renal impairment, GI bleeding or ulcers, increased blood pressure

Major Drug Interactions

Drugs Affecting Hydrocodone–Ibuprofen

- CNS depressants: Sedation and dizziness
- CYP3A4 Inhibitors and Inducers: Alteration of hydrocodone's metabolism

Hydrocodone–Ibuprofen's Effect on Other Drugs

- Anticoagulants: Enhanced anticoagulation
- Antihypertensives: Decreased effects
- Aspirin: Increased bleeding
- CNS depressants: Additive effects
- Lithium: Increased concentration
- MAO inhibitors and SSRIs: Serotonin syndrome

Contraindications

Asthma, urticaria, or allergic-type reactions to aspirin or other NSAIDs; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

Essential Monitoring Parameters

Respiratory and mental status, blood pressure

Counseling Points

- May cause drowsiness and impair your ability to operate machinery
- May cause constipation, requiring laxatives
- Avoid alcohol use
- May cause physical or psychological dependence with prolonged use
- After prolonged use, abrupt discontinuation may result in an abstinence syndrome
- Notify your healthcare provider if pain is unrelieved

Key Points

- **Black Box Warnings:**
  - NSAIDs cause an increased risk of serious (and potentially fatal) adverse cardiovascular thrombotic events, including fatal MI and stroke. Risk may occur early during treatment and may increase with duration of use.
  - NSAIDs cause an increased risk of serious gastrointestinal inflammation, ulceration, bleeding, and

perforation (may be fatal); elderly patients and patients with history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. These events may occur at any time during therapy and without warning.
  - Use is contraindicated in the setting of coronary artery bypass graft (CABG) surgery
  - Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of hydrocodone–ibuprofen and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosage and durations to the minimum required and follow patients for signs and symptoms of respiratory depression and sedation.
  - Use with all CYP3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitant CYP3A4 inducer may result in increased hydrocodone concentrations. Monitor patients receiving hydrocodone–ibuprofen and any CYP3A4 inhibitor or inducer.
- Schedule II controlled substance
- Do not exceed daily dosing recommendations

◉ Oxycodone–Acetaminophen

Brand Names

Endocet, Percocet, Tylox, Xartemis XR

Generic Name

Oxycodone–acetaminophen

Rx Only

Class II controlled substance

Dosage Forms

Capsule, caplet, immediate- and extended-release tablet, oral solution

Usage

- *Extended-release: Management of acute pain, severe enough to require opioid treatment and for which alternative treatment options are inadequate*
- *Immediate-release: Management of moderate to moderately severe pain, severe enough to require an opioid analgesic and for which alternative treatments are inadequate*

Dosing

- Immediate Release: 2.5–10 mg oxycodone component PO every 6 hours as needed
- Extended-release: 2 tablets PO every 12 hours
- Maximum dose: 3000 mg acetaminophen/day
- Renal–Hepatic impairment:
  - Extended-release: Initial dose: One tablet every 12 hours
  - Immediate-release: Use with caution; renal–hepatic impairment may require dosage adjustment

Major Drug Interactions

Drugs Affecting Oxycodone–Acetaminophen

- CNS depressants: Increase sedation and dizziness
- CYP3A4 Inhibitors–Inducers: Alteration of oxycodone's metabolism
- Ethanol use: >3 drinks/day may increase risk of hepatotoxicity
- Isoniazid: May increase the risk hepatotoxicity

Oxycodone–Acetaminophen's Effect on Other Drugs

- Warfarin: Increases anticoagulant effect
- CNS depressants: Additive effect

Essential Monitoring Parameters

Respiratory and mental status, blood pressure

Counseling Points

- May cause drowsiness and impair your ability to operate machinery
- May cause constipation, requiring laxatives
- Avoid alcohol use
- May cause physical or psychological dependence with prolonged use
- Notify your healthcare provider if pain is unrelieved
- A new prescription is required for any refill

Key Points

- **Black Box Warnings:**
  - Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4 g/day, and often involve more than one acetaminophen-containing product.
  - Swallow oxycodone–acetaminophen ER whole; crushing, chewing, or dissolving oxycodone/acetaminophen ER can cause rapid release and absorption of a potentially fatal dose of oxycodone
  - Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of oxycodone–acetaminophen and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosage and durations to the minimum amount required and follow patients for signs and symptoms of respiratory depression and sedation.
  - The concomitant use of oxycodone–acetaminophen with all CYP3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse

reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used CYP3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving oxycodone–acetaminophen and any CYP3A4 inhibitor or inducer.

- Multiple combinations of oxycodone–acetaminophen are available in various strengths
- Prescriptions and orders for this drug must include the strength desired
- Schedule II controlled substance
- Do not exceed acetaminophen daily dosing recommendations

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for mild pain symptoms. They possess analgesic, anti-inflammatory, and antipyretic effects. The use of these agents is complicated by their GI side effects and cardiovascular risks. Ibuprofen and naproxen are two agents in the class that are available OTC and found in many common cold and headache formulations. NSAIDs have many characteristics in common, which are listed here.

Mechanism of Action for the Drug Class

Inhibit prostaglandin synthesis by decreasing the activity of COX enzymes 1 and 2 non-selectively, resulting in decreased formation of prostaglandin precursors associated with inflammation and pain.

Adverse Reactions for the Drug Class: Most Common

Nausea, gastritis, diarrhea, abdominal cramps, GI ulcers, peripheral edema, hypertension

Adverse Reactions for the Drug Class: Rare/Severe/Important

GI perforation and bleeding, renal toxicity, acute renal failure, angioedema, bronchoconstriction, asthma, rash, tinnitus, hearing loss

Major Drug Interactions for the Drug Class

Drugs Affecting NSAIDs

- Corticosteroids: Increased GI side effects
- Ethanol: Increased GI irritation

NSAIDs' Effects on Other Drugs

- ACE inhibitors and angiotensin II receptor blockers: Decreased antihypertensive effect; increased risk of renal toxicity
- Anticoagulants: Increased bleeding risk
- Antiplatelet therapy: Increased bleeding risk
- Beta blockers: Decreased effect
- Digoxin: Increased level
- Diuretics: Decreased diuretic effect; increased risk of renal toxicity
- Heparin: Increased anticoagulant effect
- Warfarin: Increased anticoagulant effect
- Lithium: Increased concentrations, possible toxicity

Contraindications for the Drug Class

History of allergic reaction to aspirin or other NSAIDs (asthma, urticaria), perioperative pain management in the setting of CABG surgery

Counseling Points for the Drug Class

- Be aware of the signs and symptoms of GI bleeding
- Take with food if GI upset occurs
- Report any abnormal swelling or bleeding to your healthcare provider
- Call your healthcare provider if your pain does not improve
- This medicine can increase your cardiovascular risk (except aspirin, which is cardioprotective)

Key Points for the Drug Class

- **Black Box Warnings:**
  - Contraindicated in perioperative pain management in the setting of CABG surgery (except aspirin)
  - Increased risk for thrombosis, stroke, and myocardial infarction (except aspirin)
  - Increased risk of serious GI events, including bleeding, perforation, and ulceration (except aspirin)
- GI events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers); concurrent therapy with aspirin, anticoagulants, and/or corticosteroids; smoking; use of alcohol; and elderly or debilitated patients. Concurrent use of proton pump inhibitors or histamine-2 antagonists may reduce the risk of GI ulcers in high-risk patients.
- Elderly are at increased risk for GI effects, CNS effects, and renal toxicities
- Use with caution in patients with fluid retention, congestive heart failure, renal insufficiency, or hypertension

- Use of NSAIDs can compromise renal function. Renal toxicity is more likely to occur in patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Monitor renal function closely. Not recommended for use in patients with advanced renal disease.
- Patients with hypersensitivity reactions to sulfonamides (especially nonantibiotic sulfonamides) should avoid celecoxib
- Patients with the "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk of hypersensitivity. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.

Members of the Drug Class

In this section: Aspirin, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen. Others: Diflunisal, etodolac, fenoprofen, flurbiprofen, ketoprofen, meclofenamate, mefenamic acid, nabumetone, oxaprozin, piroxicam, sulindac, tolmetin

◉ Aspirin

Brand Names

Bayer, Bufferin, Ecotrin, Excedrin, various others

Generic Name

Aspirin

OTC

Dosage Forms

Enteric-coated, buffered, chewable, and controlled-release tablets; caplets; extended-release capsule; gum; suppository

Usage

Treatment of mild to moderate pain, inflammation, and fever; prevention and treatment of MI, acute ischemic stroke, and transient ischemic episodes; adjunctive therapy in revascularization procedures (CABG, PTCA*, carotid endarterectomy), and stent implantation;* prevention of thromboembolism in atrial fibrillation; management of rheumatoid arthritis, rheumatic fever, osteoarthritis, and gout (high dose)

Pregnancy Category

No formal category, but it is contraindicated except for low doses. Aspirin crosses the placenta; adverse effects have been reported, though fetal harm has not been shown in use of low doses for necessary treatment of certain conditions in pregnancy

Dosing

- Adults:
  - Antiplatelet indications: 50–325 mg daily
  - Treatment of acute ischemic stroke or transient ischemic attack: 162–325 mg PO within 48 hours of event
  - Treatment of acute MI: 162–325 mg PO at presentation
  - Pain and fever:
    - Oral: 325–650 mg every 4 to 6 hours up to 4 g/day
    - Rectal: 300–600 mg every 4 to 6 hours up to 4 g/day
- Pediatrics < 50 kg:
  - Pain and fever: Oral, rectal: 10–15 mg/kg/dose every 4 to 6 hours, up to a total of 4000 mg/day
- Severe renal and hepatic impairment: Avoid use

Adverse Reactions: Rare/Severe/Important

Reye's syndrome (children)

Major Drug Interactions (in addition to those of the class)

Drugs Affecting Aspirin

- Ginkgo biloba: Increased antiplatelet effect
- Other NSAIDs: Increased bleeding risk

Aspirin's Effect on Other Drugs

- ACE inhibitors: Decreased antihypertensive effect
- Anticoagulants: Increased bleeding risk
- Ticagrelor: Decreased efficacy with concomitant aspirin doses of >100–150 mg daily

Contraindications

Hypersensitivity to salicylates or other NSAIDs; patients with asthma, rhinitis, and nasal polyps; do not use in children (< 16 years of age) for viral infections (chickenpox or flu symptoms), with or without fever, due to a potential association with Reye's syndrome

Counseling Points

- High-dose aspirin should only be used in the short term for pain
- Report any signs of bruising or bleeding, nausea, or vomiting to your healthcare provider
- Do not use aspirin with a strong vinegar-like odor
- Take with food or milk

Key Points

- Do not use in children during viral infections due to the potential for Reye's syndrome, a rare but life-threatening disorder associated with aspirin use during viral infections
- Caution in pregnancy (avoid in 3rd trimester), bleeding disorders, heavy ethanol use, and GI disease
- Aspirin therapy should be stopped 1 week prior to surgery to reduce bleeding risk unless otherwise indicated by physician
- Aspirin irreversibly inhibits COX-1 and 2, leading to inhibition of platelet aggregation for 7 to 10 days (lifespan of platelets)

Diclofenac

Brand Names

Zipsor, Zorvolex, Flector, Pennsaid, Solaraze, Voltaren, Dyloject, Cambia

Generic Name

Diclofenac

Rx Only

Dosage Forms

Capsule, tablet, delayed-release enteric tablet, extended-release tablet, powder for oral solution, topical gel (1%, 3%), topical solution, topical cream (1%, 2.5%) transdermal patch, ophthalmic solution, intravenous injection

Usage

Acute treatment for mild to moderate pain, dysmenorrhea, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, postoperative inflammation following eye surgery, actinic keratosis, migraine

Pregnancy Category

- Topical gel 3%: Category B
- Oral, ophthalmic, topical gel 1%, topical solution, topical patch, injection: Category C
- Oral, topical solution, injection ≥ 30 weeks gestation: Category D

Dosing

Capsules are not interchangeable with each other or with other oral dosage forms.

- Analgesia:
  - Immediate-release tablet: 50 mg PO 3 times daily
  - Immediate-release capsule, Zipsor (diclofenac potassium): 25 mg PO 4 times daily
  - Immediate-release capsule, Zorvolex (diclofenac acid): 18 mg or 35 mg 3 times daily
  - Injection: 37.5 mg IV every 6 hours as needed; maximum daily dose 150 mg
- Primary dysmenorrhea: 50 mg PO three times daily
- Rheumatoid arthritis and osteoarthritis:
  - Immediate-release tablet: 50 mg PO 2 to 3 times daily
  - Delayed-release tablet: 50 mg PO 2 to 3 times daily or 75 mg PO twice daily
  - Extended-release tablet: 100–200 mg daily
  - Immediate-release capsule, Zorvolex (diclofenac acid): 35 mg PO 3 times daily
- Ankylosing spondylitis: Delayed-release tablet 100–125 mg/day in four to five divided doses
- Migraine: Oral solution 50 mg as a single dose at the time of migraine onset
- Topical gel 1%:
  - Upper extremities: 2 g to affected area four times daily; maximum daily total body dose of 32 g (16 g per joint per day)
  - Lower extremities: 4 g to affected area four times daily; maximum daily total body dose of 32 g (8 g per joint per day)
- Topical patch: Apply one patch to painful site twice daily for acute pain
- Topical solution (1.5%): Apply 40 drops four times daily to each affected knee
- Topical solution (2%): Apply 2 pumps twice daily to each affected knee
- Cataract surgery: Instill 1 drop of ophthalmic solution into affected eye 4 times daily beginning 24 hours after cataract surgery and continuing for 2 weeks
- Corneal refractive surgery: Instill 1–2 drops of ophthalmic solution into affected eye within the hour prior to surgery, within 15 minutes following surgery, and then continue four times daily for up to 3 days
- Renal impairment:
  - Significant renal impairment (oral): use is not recommended
  - Moderate to severe renal impairment (injection): use is not recommended
- Hepatic impairment:
  - Severe hepatic impairment (oral): use lowest effective dose for shortest possible duration
  - Moderate to severe hepatic impairment (injection): use is not recommended

Contraindications

Hypersensitivity to bovine protein (capsule formulation only)

Postoperative patients with moderate to severe renal impairment who are at risk for volume depletion (injection formulation only)

Ibuprofen

Brand Names

Motrin, Advil, Midol 200, Nuprin, Caldolor, NeoProfen, others

Generic Name

Ibuprofen

OTC and Rx (Injection)

Dosage Forms

Tablet, chewable tablet, capsule, oral infant drops, oral suspension, injection

Usage

Acute treatment for mild to moderate pain, acute treatment for gout, osteoarthritis, dysmenorrhea, rheumatoid arthritis, antipyretic, patent ductus arteriosus, ankylosing spondylitis, cystic fibrosis

Pregnancy Category

No formal category; nonteratogenic effects on the fetus–neonate have been observed; use late in pregnancy

(≥30 weeks) should be avoided due to potential risk of premature closure of the ductus arteriosus

Dosing

- Adults:
  - Inflammatory disease: 400–800 mg PO three to four times a day; maximum 3200 mg/day
  - Analgesia–pain–fever–dysmenorrhea: 200–400 mg PO every 4 to 6 hours (maximum daily dose: 1200 mg, unless directed by physician; under physician supervision, daily doses ≤ 2400 mg may be used)
  - Analgesic IV: 400–800 mg every 6 hours as needed (maximum: 3200 mg/day)
  - Antipyretic IV: Initial dose of 400 mg, then every 4 to 6 hours or 100–200 mg every 4 hours as needed (maximum: 32 mg/day)
  - Analgesic, antipyretic OTC labeling: 200 mg PO every 4 to 6 hours as needed (maximum daily dose: 1200 mg/24 hours; analgesic maximum duration: 10 days; antipyretic maximum duration: 3 days)
  - Migraine OTC labeling: 400 mg at the onset of symptoms (maximum: 400 mg/24 hours)
- Children:
  - Antipyretic for ages 6 months to 12 years: 5–10 mg/kg PO every 6 to 8 hours (maximum daily dose: 40 mg/kg/day up to 1200 mg unless directed by a physician; under physician supervision, daily doses ≤ 2.4 g may be used)
  - Juvenile idiopathic arthritis (JIA) (unlabeled use): 30–50 mg/kg/day divided every 6 to 8 hours; start at lower end of dosing range and titrate upward (maximum: 2400 mg/day)
  - Analgesic: 4–10 mg/kg PO every 6 to 8 hours (maximum 40 mg/kg/day)
  - Chronic (>4 years) cystic fibrosis (unlabeled use): 20–30 mg/kg PO BID titrated to maintain serum concentration of 50–100 µg/ml
  - Patent ductus arteriosus: IV ibuprofen lysine (NeoProfen): Infants between 500–1500 g and ≤ 32 weeks gestational age should receive initial dose of ibuprofen 10 mg/kg, followed by two doses of 5 mg/kg at 24 and 48 hours. Dose should be based on birth weight.
- Renal impairment:
  - Moderate renal impairment: Use with caution (oral); use is contraindicated (injection)
  - Severe renal impairment: Use is contraindicated

Adverse Reactions: Most Common

Infant injection: Skin irritation, intraventricular hemorrhage, hypocalcemia, hypoglycemia, anemia, sepsis, apnea

Adverse Reactions: Rare/Severe/Important

Injection: Electrolyte imbalances, hemorrhage

Contraindications

Ibuprofen injection: Preterm infants with untreated proven or suspected infection; congenital heart disease where patency of the PDA is necessary for pulmonary or systemic blood flow; bleeding (especially with active intracranial hemorrhage or GI bleed); thrombocytopenia; coagulation defects; proven or suspected necrotizing enterocolitis (NEC); significant renal dysfunction

Key Points

- Black box warnings for CV events and GI events do not apply to NeoProfen
- Patients should be well hydrated prior to the administration of IV ibuprofen Ibuprofen is the drug of choice in patent ductus arteriosus

◉ Indomethacin

Brand Names

Indocin, Indocin SR, Tivorbex

Generic Name

Indomethacin

Rx Only

Dosage Forms

Capsule, extended-release capsule, injection, suspension, suppository

Usage

Moderate to severe osteoarthritis, acute gout, patent ductus arteriosus, pain and inflammation associated with rheumatoid disorders, acute bursitis–tendonitis, ankylosing spondylitis

Pregnancy Category C

Dosing

- Initial: 25–50 mg PO 2 to 3 times daily; sustained-release capsules should be given 1 to 2 times daily; maximum dose 200 mg daily
- Inflammatory–rheumatoid disorders (use lowest effective dose):
  - Oral, rectal: 25–50 mg/dose 2 to 3 times a day; maximum dose is 200 mg/day
  - Extended-release capsule: Should be given 1 to 2 times a day (maximum dose: 150 mg/day). In patients with arthritis and persistent night pain and/or morning stiffness, may give the larger portion (up to 100 mg) of the total daily dose at bedtime
- Bursitis/tendonitis, oral, rectal:
  - Initial dose: 75–150 mg/day in 3 to 4 divided doses
  - Extended-release: 1 to 2 divided doses
  - Usual treatment: 7 to 14 days
- Acute gouty arthritis, oral, rectal: 50 mg 3 times daily until pain is tolerable, then reduce dose; usual treatment < 3–5 days
- Acute pain, mild to moderate (Tivorbex only): 20 mg 3 times daily or 40 mg 2 to 3 times daily

- Patent ductus arteriosus (pediatric-only indication): 0.2 mg/kg IV followed by 2 doses depending on postnatal age
- Renal impairment: If urinaria output < 0.6 ml/kg/hour (oliguria, anuria), hold dose until renal function returns to normal
- Hepatic impairment: Use with caution in hepatic impairment

Adverse Reactions: Most Common

Infant injection: Skin irritation, intraventricular hemorrhage, hypocalcemia, hypoglycemia, anemia, sepsis, apnea

Adverse Reactions: Rare/Severe/Important

Injection: Electrolyte imbalances, hemorrhage

Contraindications

- Suppositories: History of proctitis or recent rectal bleeding
- Neonates: Necrotizing enterocolitis, impaired renal function, active bleeding, thrombocytopenia, coagulation defects, untreated infection, congenital heart disease where patent ductus arteriosus is necessary

◉ Ketorolac

Brand Names

Toradol, Sprix, Acular, Acuvail

Generic Name

Ketorolac

Rx Only

Dosage Forms

Tablet, injection, nasal spray, ophthalmic solution

Usage

Short-term management of moderate-to-severe acute pain, *postoperative pain*, ocular itching due to seasonal allergies, ocular pain, ocular surgery inflammation (ophthalmic)

Pregnancy Category

- Oral, injection, or ophthalmic: Category C Systemic use is contraindicated during labor and delivery. Systemic use late in pregnancy (≥ 30 weeks) should be avoided due to potential risk of premature closure of the ductus arteriosus
- Nasal after ≥ 30 weeks gestation: Category D

Dosing

- Acute pain:
  - IM: 60 mg as a single dose or 30 mg every 6 hours (maximum daily dose: 120 mg)
  - IV: 30 mg as a single dose or 30 mg every 6 hours (maximum daily dose: 120 mg)
  - Oral: 20 mg, followed by 10 mg PO every 4 to 6 hours; do not exceed 40 mg/day; oral dosing is intended to be a continuation of IM or IV therapy only
  - Geriatric or low body weight < 50 kg or mild to moderate renal impairment:
    - IM: 30 mg as a single dose or 15 mg every 6 hours (maximum daily dose: 60 mg)
    - IV: 15 mg as a single dose or 15 mg every 6 hours (maximum daily dose: 60 mg)
  - Oral: 10 mg, followed by 10 mg PO every 4 to 6 hours; do not exceed 40 mg/day; oral dosing is intended to be a continuation of IM or IV therapy only
- Nasal spray:
  - One spray in each nostril every 6 to 8 hours
  - Adults < 50 kg or ≥ 65 years of age: One spray in one nostril every 6 to 8 hours
- Seasonal allergic conjunctivitis (relief of ocular itching): Instill one drop (0.25 mg) of ophthalmic solution into affected eye(s) four times daily
- Inflammation following cataract extraction: Instill one drop (0.25 mg) ophthalmic solution into affected eye(s) four times daily beginning 24 hours after surgery; continue for 2 weeks
- Pain following corneal refractive surgery: Instill one drop of ophthalmic solution into affected eye(s) 4 times daily as needed for up to 4 days
- Renal impairment: See dosing for "geriatric or low body weight or mild to moderate renal impairment" above

Contraindications

Severe renal impairment; recent or history of GI bleeding or perforation; use before major surgery; suspected or confirmed cerebrovascular bleeding; labor and delivery; breastfeeding

Essential Monitoring Parameters

Renal function (serum creatinine, BUN, urine output)

Key Points

- **Black Box Warnings:**
  - Inhibits platelet function; contraindicated in patients with cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis, and in patients at high risk for bleeding
  - Contraindicated in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion
  - Concurrent use with aspirin or other NSAIDs is contraindicated due to the increased risk of adverse reactions
  - Contraindicated during labor and delivery; may inhibit uterine contractions and adversely affect fetal circulation
  - Dosage adjustment is required in patients weighing < 50 kg
  - Not indicated for use in pediatric patients
  - Oral therapy is only indicated for use as a continuation of IM or IV formulation only
  - Systemic formulations are indicated for short term (≤ 5 days) for treatment of moderately severe

acute pain requiring opioid-level analgesia; do not exceed maximum daily recommended doses; may increase adverse effects without increasing efficacy

Meloxicam

Brand Name
Mobic, Vivlodex

Generic Name
Meloxicam

Rx Only

Dosage Forms
Tablet, capsule, oral suspension

Usage
Osteoarthritis, *rheumatoid arthritis,* juvenile rheumatoid arthritis

Pregnancy Category
No formal category; nonteratogenic effects on the fetus/neonate have been observed; use late in pregnancy (≥30 weeks) should be avoided due to potential risk of premature closure of the ductus arteriosus

Dosing
- Adults:
  - Tablet–suspension: 7.5 mg PO daily up to 15 mg daily
  - Capsule: Initially 5 mg daily; may titrate to a maximum of 10 mg daily
- Children: 0.125 mg/kg per day; maximum dose 7.5 mg daily
- Renal impairment:
  - Severe impairment: Use not recommended
- Hepatic impairment:
  - Severe hepatic adjustment: Use with caution

Key Points
- Capsules are not interchangeable with tablet–suspension
- Dosage Forms even if strength is the same; do not substitute

Naproxen

Brand Names
Aleve, Anaprox, Midol ER, Naprosyn, Naprelan, various others

Generic Name
Naproxen

OTC and Rx

Dosage Forms
Tablet, capsule, extended-release tablet, delayed-release–enteric-coated tablet, gelcap, suspension

Usage
Acute treatment for mild to moderate pain, *dysmenorrhea*, *osteoarthritis,* rheumatoid arthritis, bursitis, tendonitis, acute treatment for gout, fever, migraine headaches

Pregnancy Category
No formal category; nonteratogenic effects on the fetus–neonate have been observed; use late in pregnancy (≥ 30 weeks) should be avoided due to potential risk of premature closure of the ductus arteriosus

Dosing
- Gout, acute: Initial 750 mg PO, followed by 250 mg every 8 hours until attack subsides
- Migraine, acute (unlabeled use): Initial 500–750 mg PO; an additional 250–500 mg may be given if needed; maximum: 1250 mg in 24 hours
- Pain (mild to moderate), dysmenorrhea, acute tendonitis, bursitis: Initial 500 mg PO, then 500 every 12 hours or 250 mg every 6 to 8 hours; maximum: 1,250 mg/day naproxen
- Rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis: 500–1,000 mg/day in two divided doses; may increase to 1.5 g/day of naproxen base for a limited time period
- OTC labeling for pain/fever: 200 mg naproxen base every 8 to 12 hours; if needed, may take 400 mg naproxen base for the initial dose; maximum: 400 mg naproxen base in any 8- to 12-hour period or 600 mg naproxen base over 24 hours
- Renal impairment:
  - CrCl < 30 ml/min: Avoid use

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS, SELECTIVE COX-2 INHIBITOR

Introduction

The selective COX-2 inhibitor celecoxib is commonly used for mild pain syndromes, such as arthritis, with the benefit of a lower incidence of GI ulcers than nonselective NSAIDs. Its use is complicated by a small but significant increase in cardiovascular events such as stroke and myocardial infarction. Although celecoxib has less GI toxicity than nonselective NSAIDs, many of the same warnings, adverse effects, and counseling points apply. A second agent, rofecoxib, was removed from the market in 2004 due to safety concerns.

Mechanism of Action for the Drug Class

Inhibits prostaglandin synthesis by decreasing the activity of the enzyme COX-2, which results in decreased formation of prostaglandin precursors and exhibits analgesic, anti-inflammatory, and antipyretic effects. COX-2 inhibitors do not appear to block COX-1 as extensively as nonselective NSAIDs, decreasing their toxicity to the GI mucosa.

Members of the Drug Class

Celecoxib

⦿ Celecoxib

Brand Name

Celebrex

Generic Name

Celecoxib

Rx Only

Dosage Form

Capsule

Usage

Relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis (JIA); management of acute pain; treatment of primary dysmenorrhea; acute gout

Pregnancy Category

Category C < 30 weeks' Gestation and Category D ≥ 30 weeks' Gestation

Dosing

- Osteoarthritis: 200 mg/day PO as a single dose or in divided doses twice daily
- Rheumatoid arthritis: 100–200 mg PO twice daily
- Acute pain or primary dysmenorrhea:
  - Initial dose: 400 mg PO, followed by an additional 200 mg PO, if needed on day 1
  - Maintenance dose: 200 mg PO twice daily as needed
- Ankylosing spondylitis:
  - Initial dose: 200 mg/day PO as a single dose or in divided doses twice daily
  - If no effect after 6 weeks, may increase to 400 mg/day
  - If no response following 6 weeks of treatment with 400 mg/day, consider discontinuation and alternative treatment
- Renal impairment: Avoid in advanced renal disease
- Hepatic impairment: Reduce dose by 50% in moderate impairment; not recommended in severe impairment

Adverse Reactions: Most Common

Nausea, diarrhea, GI ulcers, hypertension, headache, peripheral edema

Adverse Reactions: Rare/Severe/Important

GI ulcers, bleeding, and perforation; thrombosis, MI, and stroke; acute renal failure; erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis; fulminant hepatitis and liver failure

Major Drug Interactions

Drugs Affecting Celecoxib

- Antacids: Decreased absorption of celecoxib
- Corticosteroids: Increased GI side effects
- Ethanol: Increased GI irritation
- Fluconazole: Increased concentrations of celecoxib

Celecoxib's Effect on Other Drugs

- ACE inhibitors and angiotensin II receptor blockers: Decreased antihypertensive effect; increased risk of renal toxicity
- Anticoagulants: Increased bleeding risk
- Aspirin: Increased bleeding risk; decreased cardioprotective effect
- Cyclosporine: Increased cyclosporine levels
- Diuretics: Decreased effects; increased risk of renal toxicity
- Lithium: Increased concentrations

Contraindications

Hypersensitivity to sulfonamides, aspirin, and other NSAIDs; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

Counseling Points

- Be informed about signs and symptoms of GI bleeding
- Take with food if GI upset occurs
- Report any abnormal swelling or bleeding to your healthcare provider

- Call your healthcare provider if your pain does not improve
- This medicine can increase your cardiovascular risk

Key Points

- **Black Boxed Warnings:**
  - Contraindicated in perioperative pain management in the setting of CABG surgery
  - Increased risk for thrombosis, stroke, and myocardial infarction
  - Increased risk of serious GI events including bleeding, perforation, and ulceration
- GI events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers); concurrent therapy with aspirin, anticoagulants, and/or corticosteroids; smoking; use of alcohol; and elderly or debilitated patients.
- Celecoxib does not inhibit platelets or prolong bleeding time
- Elderly are at increased risk for GI effects, CNS effects, and renal toxicities
- Use with caution in patients with fluid retention, congestive heart failure, renal insufficiency, or hypertension
- Use of NSAIDs can compromise renal function. Renal toxicity is more likely to occur in patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Monitor renal function closely. Not recommended for use in patients with advanced renal disease.
- Patients with hypersensitivity reactions to sulfonamides (especially nonantibiotic sulfonamides) should avoid celecoxib
- Patients with the "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk of hypersensitivity. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.

MISCELLANEOUS ANALGESICS

Introduction

Two commonly used analgesics fall into categories of their own and are discussed here. Acetaminophen, one of the most commonly used analgesics and antipyretics, is generally well tolerated but noted for its hepatotoxicity when given in doses that exceed daily recommendations. Butalbital combinations are most frequently used to treat headaches.

Mechanism of Action for the Drug Class

Acetaminophen inhibits brain prostaglandin synthesis, leading to analgesic and antipyretic activity. Butalbital is a barbiturate that depresses the sensory cortex and motor activity, producing sedation and drowsiness. Caffeine increases cAMP and acts as a vasoconstrictor and CNS stimulant, though it does not exhibit any analgesic properties on its own. The combination is commonly used to treat headaches.

Members of the Drug Class

In this section: Acetaminophen, butalbital with caffeine and acetaminophen
Others: Butalbital with acetaminophen; butalbital with caffeine, acetaminophen, and codeine; butalbital with caffeine and aspirin; butalbital with caffeine, aspirin, and codeine

◉ Acetaminophen

Brand Names

Tylenol, Paracetamol, Ofirmev (injectable), various others

Generic Name

Acetaminophen

OTC and Rx Only

Noninjectable: OTC; Injection: Rx Only

Dosage Forms

Tablet (oral, chewable, disintegrating, and extended-release), capsule, caplet, gelcap, elixir, solution, suspension, suppository, injection (Rx Only)

Usage

Fever, mild pain such as headaches and arthritis pain, combined with other analgesics for moderate to severe pain

Pregnancy Category

No formal category; acetaminophen crosses the placenta; an increased risk of teratogenic effects has not been observed following maternal use of acetaminophen

Dosing

- Oral: Usual dose: 500–650 mg PO every 4 to 6 hours as needed; maximum daily dose varies by formulation
  - Immediate-release:
    - Regular strength: 650 mg PO every 4 to 6 hours; maximum daily dose 3250 mg
    - Extra strength: 1000 mg PO every 6 hours; maximum daily dose: 3000 mg
  - Extended-release: 1300 mg PO every 8 hours; maximum daily dose 3900 mg

- Maximum daily dose under healthcare provider supervision: 4000 mg/day
- Rectal:
  - 650 mg rectally every 4 to 6 hours
    - Maximum 6 doses in 24 hours
- IV:
  - < 50 kg: 15 mg/kg IV every 6 hours or 12.5 mg/kg IV every 4 hours
    - Maximum single dose: 750 mg
    - Maximum daily dose: 75 mg/kg/day or 3750 mg/day
  - > 50 kg: 1000 mg IV every 6 hours or 650 mg IV every 4 hours
    - Maximum single dose: 1000 mg
    - Maximum daily dose: 4000 mg/day
- Children:
  - Age > 12 years: Refer to adult dosing
  - Age < 12 years:
  - Oral:
    - 10–15 mg/kg per dose PO every 4 to 6 hours as needed
    - Do not exceed 5 doses in 24 hours
  - IV:
    - 15 mg/kg IV every 6 hours or 12.5 mg/kg IV every 4 hours
    - Maximum single dose: 15 mg/kg
    - Maximum daily dose: 75 mg/kg
  - Rectal: < 12 years 10–20 mg/kg rectally every 4 to 6 hours as needed
- Renal impairment (oral, adults):
  - CrCl 10–50 ml/min: Administer every 6 hours
  - CrCl < 10 ml/min: Administer every 8 hours
- Hepatic impairment: Use with caution

Adverse Reactions: Most Common

Well-tolerated at therapeutic doses

Adverse Reactions: Rare/Severe/Important

Hepatotoxicity, particularly with higher than recommended dosing

Major Drug Interactions

Drugs Affecting Acetaminophen

- Carbamazepine: Increased risk of hepatotoxicity, decreased effect of acetaminophen
- Ethanol use: >3 drinks/day may increase risk of hepatotoxicity
- Isoniazid: Increased risk of hepatotoxicity
- Phenytoin: Increased risk of hepatotoxicity

Acetaminophen's Effect on Other Drugs

Warfarin: Increased anticoagulant effect

Contraindications

Severe hepatic impairment or severe active liver disease

Essential Monitoring Parameters

Signs of hepatotoxicity, including dark urine, abdominal pain, and elevated liver function tests

Counseling Points

- Report unresolved pain or fevers to your healthcare provider
- Adults: Maximum daily doses vary by formulation; do not exceed 4000 mg/day under supervision of healthcare provider; less than 3000 mg/day for chronic dosing
- Use weight-based dosing in children with appropriate accompanying measuring device for liquid formulations
- Shake suspension well before pouring
- Extended-release products must be swallowed whole, not chewed or crushed

Key Points

- **Black Box Warnings:**
  - Life-threatening acute hepatic failure, mostly when acetaminophen doses exceeded recommended daily limits
  - Injection dosing errors; be sure doses in milligrams (mg) are not confused with doses in milliliters (ml), patients < 50 kg receive weight-based dosing, infusion pumps are programmed correctly, and total dose of acetaminophen from all sources does not exceed recommended daily limits
- Adherence to maximum daily dose recommendations is important to avoid hepatotoxicity
- Many OTC cold, sleep, and pain products and prescription opioid analgesic combinations contain acetaminophen. Patients should be warned to avoid inadvertently overdosing on acetaminophen by combining products that contain it
- Careful consideration should be taken when measuring out a pediatric dose from a liquid formulation to ensure correct dosing. Liquid concentrations in formulations have changed to decrease the likelihood for errors
- Acetaminophen is the preferred analgesic during pregnancy and breastfeeding

Butalbital with Caffeine and Acetaminophen

Brand Names

Fioricet, Zebutal, various others

Generic Names

Butalbital, acetaminophen, and caffeine

Rx Only

Class III controlled substance

Dosage Forms

Tablet, capsule, oral liquid

Butalbital 50 mg, Acetaminophen 300–325 mg, Caffeine 40 mg per tablet, capsule or 15 ml liquid

Usage

Relief of tension or muscle contraction headaches

Pregnancy Category C

Dosing

- Tension or muscle contraction headache:
  - One to 2 tablets or capsules (or 15–30 ml solution) every 4 hours
  - Do not exceed 6 tablets or capsules (or 180 ml liquid) daily
- Renal impairment: Use with caution in severe renal impairment
- Hepatic impairment: Use with caution in severe hepatic impairment

Adverse Reactions: Most Common

Dizziness, drowsiness, nausea

Adverse Reactions: Rare/Severe/Important

Respiratory and CNS depression, hepatotoxicity (exceeding acetaminophen dosing recommendations)

Major Drug Interactions

Drugs Affecting Butalbital with Caffeine and Acetaminophen

- CNS depressants: May enhance the adverse–toxic effect of other CNS depressants, such as opioid analgesics or benzodiazepines
- Ethanol use: >3 drinks/day may increase risk of hepatotoxicity
- Isoniazid: May increase the risk of hepatotoxicity
- Somatostatin: May enhance or prolong effects such as sedation

Butalbital with Caffeine and Acetaminophen's Effect on Other Drugs

Increases the metabolism of calcium channel blockers, contraceptives, cyclosporine, doxycycline, tricyclic antidepressants, ulipristal, voriconazole, warfarin

Contraindications

Porphyria

Counseling Points

- Report unresolved headache to your healthcare provider
- Do not use more than the recommended daily dose

Key Point

- Many OTC cold, sleep, and pain products and prescription opioid analgesic combinations contain acetaminophen. Patients should be warned to avoid inadvertently overdosing on acetaminophen by taking them in excessive combinations.

REVIEW QUESTIONS

1. Which of the following is a contraindication to all narcotic analgesics?
   - **a.** Severe respiratory disease or depression, including acute asthma (unless patient is mechanically ventilated)
   - **b.** Uncontrolled hypertension
   - **c.** Concomitant use of topical steroids
   - **d.** Active smoking history

2. Which of the following is true regarding buprenorphine?
   - **a.** Buprenorphine is a nonsteroidal anti-inflammatory (NSAID)
   - **b.** Buprenorphine is Pregnancy Category C
   - **c.** Buprenorphine is not available in a transdermal patch formulation
   - **d.** Buprenorphine does not have hepatic dose adjustments

3. Which if the following is false regarding fentanyl?
   - **a.** Fentanyl is a Class III controlled substance
   - **b.** Dosage Forms of fentanyl include nasal spray, sublingual spray, sublingual tablets, and injection
   - **c.** Fentanyl is Pregnancy Category C
   - **d.** Common adverse effects of fentanyl include constipation, nausea, vomiting, and sedation

4. Which of the following is an appropriate starting dose of hydromorphone immediate release oral formulation?
   - **a.** 16 mg PO every 4 hours as needed
   - **b.** 9 mg PO every 2 hours as needed
   - **c.** 12 mg PO every 6 hours as needed
   - **d.** 2 mg PO every 4 hours as needed

5. Which of the following is NOT an example of a drug-drug interaction with methadone?
   - **a.** Nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs): Reduce methadone levels
   - **b.** CYP3A4 inducers: Reduce methadone levels
   - **c.** Stavudine and didanosine: increase methadone bioavailability
   - **d.** CYP3A4 inhibitors: Increase methadone levels

6. Which of the following is NOT a brand name of morphine?
   - **a.** Kadian
   - **b.** Dolophine
   - **c.** MS Contin
   - **d.** Oramorph SR

7. Which of the following includes all available Dosage Forms of oxycodone?
   a. Capsule, oral liquid, oral concentrate, immediate- and controlled-release tablets
   b. Capsule, oral liquid, oral concentrate, immediate-release tablets
   c. Tablet, oral liquid, immediate-release tablets, transdermal patch
   d. Tablet, oral concentrate, immediate-release tablets, transdermal patch

8. Zohydro ER and Hysingla ER are brand names of which of the following medications?
   a. Methadone
   b. Oxycodone
   c. Hydrocodone
   d. Hydromorphone

9. Which of the following is a contraindication of tapentadol?
   a. Use of MAO inhibitors within 14 days
   b. Concomitant use of ibuprofen
   c. Myocardial infarction within the last 30 days
   d. Uncontrolled hypertension

10. Which of the following would be an appropriate renal dose adjustment for tramadol in a patient whose creatinine clearance is less than 30 ml/min?
    a. Increase to 200 mg every 12 hours
    b. Increase dosing interval to every 12 hours (maximum: 200 mg/day)
    c. Decrease to 10 mg every 24 hours
    d. Decrease to 50 mg every 8 hours

11. Which of the following statements is true regarding narcotic–nonnarcotic combinations?
    a. The narcotic component binds to opioid μ-receptors, altering the perception and response to pain. The nonnarcotic analgesic inhibits brain prostaglandin synthesis.
    b. The narcotic component is a partial agonist of μ- and κ-receptors, altering the perception and response to pain. The nonnarcotic analgesic binds to opioid μ-receptors.
    c. The narcotic component inhibits brain prostaglandin synthesis, altering the perception and response to pain. The nonnarcotic analgesic inhibits the reuptake of norepinephrine.
    d. The narcotic component inhibits brain prostaglandin synthesis, altering the perception and response to pain. The nonnarcotic analgesic binds to opioid μ-receptors.

12. Which of the following is a rare, serious adverse effect of codeine–acetaminophen?
    a. Dizziness
    b. Xerostomia
    c. Pruritus
    d. Hallucinations

13. Which of the following is an appropriate starting dose of hydrocodone–acetaminophen for a 6-year-old patient weighing 60 kg?
    a. 5 mg hydrocodone component every 4 to 6 hours
    b. 15 mg hydrocodone component every 4 to 6 hours
    c. 5 mg hydrocodone component every 4 to 6 hours
    d. 15 mg hydrocodone component every 1 to 2 hours

14. Hydrocodone–ibuprofen is contraindicated in which of the following situations?
    a. Stroke within the last 30 days
    b. Active smoking history
    c. Asthma, urticaria, or allergic reactions to aspirin or other NSAIDs
    d. Concomitant use of lidocaine patches

15. Endocet and Percocet are brand names of which of the following medications?
    a. Hydromorphone
    b. Methadone
    c. Oxycodone–acetaminophen
    d. Oxycodone–ibuprofen

16. Which of the following is the maximum daily dosage for acute acetaminophen use in most healthy adults under the supervision of a healthcare provider?
    a. 2000 mg
    b. 3000 mg
    c. 4000 mg
    d. 5000 mg

17. It is important to account for dosage of acetaminophen from all sources (including common OTC combination products) because excessive dosing could lead to which adverse effect?
    a. Renal toxicity
    b. Hepatotoxicity
    c. GI bleeding
    d. Respiratory depression

18. Butalbital is commonly used for which of the following?
    a. Fever
    b. Gout
    c. Osteoarthritis
    d. Tension headache

19. Which of the following is an advantage of celecoxib over other NSAIDs?

- **a.** Less GI events
- **b.** Safer in pregnancy
- **c.** Fewer CV events
- **d.** Safer in renal impairment

20. Black box warnings for GI events, CV events, and use in CABG surgery apply to all NSAIDs *except* which of the following?

- **a.** Aspirin
- **b.** Ibuprofen
- **c.** Ketorolac
- **d.** Meloxicam

21. Which of the following risk is the reason NSAIDs should be avoided at ≥ 30 weeks of pregnancy?

- **a.** Miscarriage
- **b.** Teratogenicity
- **c.** Premature labor
- **d.** Premature closure of the ductus arteriosus

22. Concomitant use of NSAIDs and ACE inhibitors can increase the risk of which of the following?

- **a.** Renal toxicity
- **b.** Hepatotoxicity
- **c.** Bleeding
- **d.** Hypotension

23. Which of the following is appropriate ibuprofen dosing for analgesia in children < 12 years?

- **a.** 4–10 mg/kg/dose every 6 to 8 hours
- **b.** 20–30 mg/kg/dose BID
- **c.** 30–50 mg/kg/day every 6 to 8 hours
- **d.** 200 mg PO every 6 to 8 hours

24. Which of the following is the drug of choice for patent ductus arteriosus?

- **a.** Celecoxib
- **b.** Ibuprofen
- **c.** Indomethacin
- **d.** Ketorolac

25. Which of the following is true regarding systemic ketorolac?

- **a.** Treatment should not exceed 3 days; contraindicated in patients with severe renal impairment
- **b.** Treatment should not exceed 5 days; maximum single IV dose for healthy adults is 60 mg
- **c.** Oral therapy is only indicated for use as continuation of IM or IV; contraindicated in patients with severe renal impairment
- **d.** Oral therapy is only indicated for use as continuation of IM or IV; maximum single IV dose for healthy adults is 15 mg

26. Use of NSAIDs with lithium can result in which of the following?

- **a.** Increased concentration of lithium
- **b.** Decreased concentration of lithium
- **c.** Increased concentration of NSAIDs
- **d.** Decreased concentration of NSAIDs

27. Which of the following is correct dosing of aspirin for acute MI?

- **a.** 81 mg PO STAT
- **b.** 100 mg PO STAT
- **c.** 325 mg PO STAT
- **d.** 650 mg PO STAT

28. Diclofenac comes in which of the following nonoral Dosage Forms?

- **a.** Transdermal patch
- **b.** Transdermal patch, topical gel
- **c.** Transdermal patch, topical gel, ophthalmic solution
- **d.** Transdermal patch, topical gel, ophthalmic solution, intravenous injections

29. Which of the following is correct initial dosing of indomethacin for acute gouty arthritis?

- **a.** 25 mg PO two times a day
- **b.** 25 mg PO three times a day
- **c.** 50 mg PO two times a day
- **d.** 50 mg PO three times a day

30. Using aspirin in children with viral infections is associated with which of the following severe adverse effects?

- **a.** Anaphylaxis
- **b.** Renal failure
- **c.** Reye's syndrome
- **d.** Necrotizing enterocolitis

CHAPTER 2

Antidiabetic Agents

Charles Ruchalski, PharmD, BCPS

BIGUANIDES

Introduction

For newly diagnosed patients with type 2 diabetes, the biguanide metformin is the drug of choice for initial therapy, adjunctive to diet and exercise. It is often used in combination with other oral antidiabetic agents and/or insulin in patients who do not reach glycemic goals on those therapies. HbA1c reductions with metformin are generally between 1.5% and 2%. Metformin is contraindicated in certain patients to prevent lactic acidosis, a rare but serious side effect (approximately 0.03 cases per 1000 patient-years, with approximately 0.015 fatal cases per 1000 patient-years).

Mechanism of Action for the Drug Class

Biguanides improve glucose tolerance by lowering both basal and postprandial plasma glucose. They decrease hepatic glucose production and intestinal absorption of glucose and improve insulin sensitivity by increasing peripheral glucose uptake and utilization through the activation of adenosine monophosphate-activated protein kinase (AMPK).

◉ Metformin

Brand Names

Fortamet, Glucophage, Glucophage XR, Glumetza, Riomet, D-Care DM2

Generic Names

Metformin, metformin extended-release

Rx Only

Dosage Forms

Tablet, extended-release tablet, oral solution

Usage

Type 2 diabetes mellitus, prevention of type 2 diabetes mellitus, gestational diabetes, polycystic ovary syndrome, antipsychotic-induced weight gain

Pregnancy Category B

Dosing

- Initial dose: 500 mg twice daily with morning and evening meals, 850 mg once daily with a meal, or 500 mg extended-release once daily with a meal
- Maintenance dose: 2000–2550 mg daily in divided doses or 2000 mg extended-release once daily (2500 mg daily with Fortamet)
- Renal dosage adjustment: GFR: > 45 ml/min: no dosage adjustment necessary, GFR: 30–45 ml/min: 50% dose reduction, GFR <30 ml/min, Use is contraindicated

Adverse Reactions: Most Common

Diarrhea, vomiting, dyspepsia, flatulence, metallic taste, weight loss

Adverse Reactions: Rare/Severe/Important

Lactic acidosis, megaloblastic anemia

Major Drug Interactions

Drugs Affecting Metformin

- Alcohol potentiates the effect on lactate metabolism
- Cimetidine increases plasma concentrations (use alternative H2 blocker)
- Iodinated contrast media can lead to acute renal failure and metformin toxicity

Contraindications

GFR < 30 ml/min, acute or chronic metabolic acidosis

Essential Monitoring Parameters

HbA1c at least twice a year, serum glucose, renal function

Counseling Point

- Discontinue immediately and promptly notify healthcare practitioner if unexplained myalgia, malaise, hyperventilation, or unusual somnolence occur because those are symptoms of lactic acidosis

Key Points

- **Black Box Warnings:**
  - Lactic acidosis. (This rare but serious metabolic complication can occur; when it occurs, it is fatal 50% of the time)
  - Temporarily withhold in patients undergoing radiologic procedures involving the parenteral administration of iodinated contrast media because it may result in acute alteration of renal function. Do not restart for at least 48 hours or until renal function appears adequate.

DI-PEPTIDYL PEPTIDASE-4 INHIBITORS

Introduction

Di-peptidyl peptidase-4 (DPP-4) inhibitors inhibit the breakdown of active Glucagon-Like Peptide-1 (GLP-1) to inactive GLP-1 through the inhibition of the DPP-4 enzyme. Active GLP-1 is released from the alpha cells of the pancreas in response to food intake. GLP-1 plays a role in regulating blood glucose by increasing the secretion of insulin from the pancreas in a glucose-dependent manner. GLP-1 also helps regulate glucagon secretion and decreases hepatic glucose production. Those drugs are used as monotherapy as an adjunct to diet and exercise or in combination with other oral antidiabetic agents in patients who do not reach glycemic goals. Average HbA1c reductions are between 0.7% and 1%.

Mechanism of Action for the Drug Class

Inhibition of DPP-4 enhances the activity of active GLP-1, thus increasing glucose-dependent insulin secretion and decreasing levels of circulating glucagon and hepatic glucose production

Members of the Drug Class

In this section: Sitagliptin
Others: Alogliptin, linagliptin, saxagliptin

◉ Sitagliptin

Brand Name

Januvia

Generic Name

Sitagliptin

Rx Only

Dosage Form

Tablet

Usage

Type 2 diabetes mellitus

Pregnancy Category B

Dosing

- 100 mg once daily with or without food
- Renal dosage adjustment:
  - 50 mg once daily: GFR ≥ 30 to < 50 ml/min
  - 25 mg once daily: GFR < 30 ml/min

Adverse Reactions: Most Common

Nasopharyngitis, nausea, diarrhea, vomiting, hypoglycemia, weight loss

Adverse Reactions: Rare/Severe/Important

Acute pancreatitis, arthralgia, bullous pemphigoid, rash (Stevens-Johnson syndrome)

Major Drug Interactions

Sitagliptin's Effect on Other Drugs

Digoxin: Increased levels

Contraindications

Severe hypersensitivity reactions

Essential Monitoring Parameters

HbA1c at least twice a year, serum glucose, renal function

Counseling Point

Discontinue immediately and promptly notify healthcare practitioner if unexplained persistent nausea and vomiting occur (signs of acute pancreatitis)

GLUCAGON-LIKE PEPTIDE-1 AGONIST

Introduction

Active Glucagon-Like Peptide-1 (GLP-1) is released from the alpha cells of the pancreas in response to food intake. GLP-1 plays a role in regulating blood glucose by increasing the secretion of insulin from the pancreas in a glucose-dependent manner. GLP-1 also helps regulate glucagon secretion and decreases hepatic glucose production. These drugs are used as monotherapy as an adjunct to diet and exercise or in combination with other oral antidiabetic agents in patients who do not reach glycemic goals. Average HbA1c reductions are between 0.5% and 1% with immediate release and 1.5% to 2% with extended release.

Mechanism of Action for the Drug Class

Glucagon-Like Peptide-1 (GLP-1) agonist enhances glucose-dependent insulin secretion and decreases levels of circulating glucagon and hepatic glucose production

Usage

Type 2 diabetes mellitus

Adverse Reactions for the Drug Class: Most Common

Hypoglycemia (when used with other oral antidiabetic drugs that may cause hypoglycemia), nausea, diarrhea, vomiting, hyperhidrosis, constipation, injection-site reactions

Adverse Reactions for the Drug Class: Rare/Severe/Important

Increased incidence of Thyroid C-Cell tumors, acute pancreatitis, acute renal failure

Major Drug Interactions for the Drug Class

Glucagon-Like Peptide-1 (GLP-1) Effects on Other Drugs

Oral contraceptives: Decreased efficacy
Warfarin: Enhanced efficacy

Contraindications for the Drug Class

Family history of medullary thyroid carcinoma or patients with multiple endocrine neoplasia syndrome

Essential Monitoring Parameters

HbA1c at least twice a year, serum glucose, renal function, GI distress, injection-site reactions

Key Point

- **Black Box Warning:**
  - Dose-dependent and treatment-duration-dependent Thyroid C-cell tumors, including medullary thyroid carcinoma

Counseling Point for the Drug Class

- Discontinue immediately and promptly notify healthcare practitioner if unexplained persistent nausea and vomiting occur (signs of acute pancreatitis)

Members of the Drug Class

In this section: Exenatide and liraglutide
Others: Albiglutide, dulaglutide, and lixisenatide

Exenatide

Brand Names

Byetta, Bydureon

Generic Names

Exenatide and Exenatide ER

Rx Only

Dosage Form

Sub-Q injection

Pregnancy Category C

Dosing

- Initial dose: Immediate-release: (Byetta) 5 µg twice daily within 60 minutes prior to a meal, extended-release: (Bydureon) 2 mg once weekly
- Maintenance dose: Immediate-release: (Byetta) 10 µg twice daily; extended-release: (Bydureon) 2 mg once weekly
- Renal dosage adjustment: GFR < 30 ml/min, Use is contraindicated

Liraglutide

Brand Names

Victoza, Saxenda

Generic Name

Liraglutide

Rx Only

Dosage Form

Sub-Q injection

Usage

Type 2 diabetes mellitus (Victoza), weight loss as an adjunct to diet and exercise (Saxenda)

Pregnancy Category C

Dosing

- Initial dose: 0.6 mg once daily for 1 week, then 1.2 mg once weekly
- Maintenance dose: 1.2 mg to 1.8 mg once weekly
- Renal dosage adjustment: No dosage adjustment necessary

INSULIN

Introduction

The hormone insulin is endogenously released from the beta cells of the pancreas. Patients with type 1 diabetes mellitus have an absolute deficiency of insulin; patients with type 2 diabetes mellitus may also have decreased production of endogenous insulin. Type 1 diabetics require insulin as a lifelong treatment. Insulin is commonly used in type 2 diabetic patients as either adjunct therapy to oral antidiabetic agents or as monotherapy as the disease progresses. Various substitutions on the insulin molecule and other modifications have led to multiple types of insulin. They are characterized and administered based on their pharmacodynamic and pharmacokinetic characteristics, such as onset, peak, and duration of action. The various types of insulin are classified as rapid-acting, short-acting, intermediate-acting, or long-acting insulin.

Mechanism of Action for the Drug Class

Insulin lowers blood glucose by stimulating peripheral glucose uptake, especially in skeletal muscle and fat, and by inhibiting hepatic glucose production

Usage for the Drug Class

Type 1 diabetes mellitus, type 2 diabetes mellitus, hyperkalemia, diabetic ketoacidosis/diabetic coma

Dosing for the Drug Class

- Initial dose: 0.5–1 unit/kg per day SUB-Q (high interpatient variability)
- Maintenance dose: Adjust doses to achieve premeal blood glucose levels of 80–130 mg/dl
- Renal dosage adjustment:
  - GFR 10–50 ml/min: Administer 75% of normal dose
  - GFR < 10 ml/min: Administer 25–50% of normal dose; monitor closely

Adverse Reactions for the Drug Class: Most Common

Hypoglycemia (anxiety, blurred vision, palpitations, shakiness, slurred speech, sweating), weight gain

Adverse Reactions for the Drug Class: Rare/Severe/Important

Severe hypoglycemia (seizure/coma), edema, lipoatrophy or lipohypertrophy at injection site

Major Drug Interactions for the Drug Class

Drugs Affecting Insulin (Decreased Hypoglycemic Effect)

- Acetazolamide
- Diuretics
- Oral contraceptives
- Albuterol
- Epinephrine
- Phenothiazines
- Asparaginase
- Estrogens
- Terbutaline
- Corticosteroids
- HIV antivirals
- Thyroid hormones
- Diltiazem
- Lithium

Drugs Affecting Insulin (Increased Hypoglycemic Effect)

- Alcohol
- Fluoxetine
- Anabolic steroids
- Lithium
- Beta blockers
- Sulfonamides
- Clonidine

Contraindications for the Drug Class

Severe hypoglycemia; allergy or sensitivity to any ingredient of the product

Essential Monitoring Parameters for the Drug Class

HbA1c at least twice a year, serum glucose, renal function, injection-site reactions

Counseling Points for the Drug Class

- Follow a prescribed diet and exercise regularly
- Rotate injection sites to prevent lipodystrophy
- Insulin requirements may change during times of illness, vomiting, fever, and emotional stress
- Wear diabetic identification
- Insulin stored at room temperature will be less painful to inject compared with refrigerator-stored insulin
- Mild episodes of hypoglycemia may be treated with oral glucose or carbohydrates

Members of the Drug Class

In this section: Insulin inhalation powder, insulin glulisine, insulin lispro, insulin NPH, insulin (R), insulin glargine, insulin detemir, insulin aspart, various mixtures are also available

◉ Insulin inhalation powder

Brand Name

Afrezza

Generic Name

Insulin inhalation powder

Rx Only

Dosage Form

Powder, inhalation (4-unit, 8-unit, and 12-unit cartridges)

Pregnancy Category C

Dosing
Administer inhalation at the beginning of each meal. Start with four units for insulin-naïve patients.

Adverse Reactions: Most Common
Hypoglycemia, cough, throat irritation

Contraindications
Hypersensitivity to regular insulin, chronic lung disease (such as asthma or COPD)

Key Points
- **Black Box Warnings:**
  - Acute bronchospasm has been observed in patients with asthma and COPD. Contraindicated in patients with chronic lung disease (such as asthma or COPD).
  - Before initiating, perform spirometry (FEV1) in all patients and assess every 6 months to 1 year. Avoid use in patients with active lung cancer.

Insulin Glulisine

Brand Names
Apidra, Apidra SoloSTAR

Generic Name
Insulin glulisine (rapid-acting insulin)

Rx Only

Dosage Form
Injection 100 units/ml (10 ml vial and 3 ml cartridge for pen use)

Pregnancy Category C

Dosing
- Administer SUB-Q 15 minutes before or immediately after starting a meal
- May be administered by continuous subcutaneous infusion (insulin pump)

Insulin Lispro

Brand Names
Humalog, Humalog KwikPen

Generic Name
Insulin lispro (rapid-acting insulin)

Rx Only

Dosage Forms
Injection 100 units/ml, 200 units/ml (10 ml vial and 3 ml cartridge for pen use)

Pregnancy Category B

Dosing
- Administer SUB-Q 15 minutes before or immediately after starting a meal
- May be administered by continuous subcutaneous infusion (insulin pump)

Insulin NPH

Brand Names
Humulin N, Novolin N

Generic Name
Insulin NPH (intermediate-acting insulin)

OTC

Dosage Forms
Injection, suspension, 100 units/ml (10 ml vial and 3 ml cartridge for pen use)

Pregnancy Category B

Dosing
- NPH should only be mixed with regular insulin
- Draw regular insulin into the syringe first, then add the NPH insulin to the syringe

Insulin Regular

Brand Names
Humulin R, Novolin R

Generic Name
Insulin regular (short-acting insulin)

OTC

Dosage Forms
Injection 100 units/ml (10 ml vial and 3 ml cartridge for pen use)
Injection 500 units/ml (20 ml vial and 3 ml cartridge for pen use) (Humulin R)

Pregnancy Category B

Dosing
- Administer SUB-Q 30 minutes before a meal
- May be administered by continuous subcutaneous infusion (insulin pump)
- Humulin R U-500 should be prescribed only for patients who require more than 200 units of insulin per day

70% NPH and 30% Regular Insulin Mixture

Brand Names
Humulin 70/30, Novolin 70/30

Generic Name
70% NPH and 30% regular insulin mixture

OTC

Dosage Forms
Injection, suspension, 100 units/ml (10 ml vial and 3 ml cartridge for pen use)

Pregnancy Category B

50% NPH and 50% Regular Insulin Mixture

Brand Name
Humulin 50/50

Generic Name
50% NPH and 50% regular insulin mixture

OTC

Dosage Forms
Injection, suspension, 100 units/ml (10 ml vial and 3 ml cartridge for pen use)

Pregnancy Category B

75% Intermediate-Acting Lispro Suspension and 25% Rapid-Acting Lispro Solution

Brand Name
Humalog Mix 75/25

Generic Name
75% intermediate-acting lispro suspension and 25% rapid-acting lispro solution

Rx Only

Dosage Forms
Injection 100 units/ml (10 ml vial and 3 ml cartridge for pen use)

Pregnancy Category B

Insulin Glargine

Brand Names
Basaglar, Lantus, Lantus SoloSTAR, Toujeo SoloSTAR

Generic Name
Insulin glargine

Rx Only

Dosage Forms
Injection 100 units/ml (10 ml vial and 3 ml cartridge for pen use)
Injection 300 units/ml (1.5 ml disposable pen) (Tuejo)

Pregnancy Category C

Dosing
- When changing to insulin glargine from once-daily NPH, the initial dose of insulin glargine should be the same. When changing to insulin glargine from twice-daily NPH, the initial dose of insulin glargine should be reduced by 20% and adjusted according to patient response.
- Administer once daily
- Starting dose in a type 2 diabetic patient is 10 units at bedtime and then titrate according to patient response

Insulin Detemir

Brand Names
Levemir, Levemir FlexPen, Levemir FlexTouch

Generic Name
Insulin detemir (long-acting insulin)

Rx Only

Dosage Forms
Injection 100 units/ml (10 ml vial and 3 ml cartridge for pen use)

Pregnancy Category B

Dosing
- Indicated for once-daily or twice-daily dosing
- Once daily is dosed with the evening meal or at bedtime
- Twice daily is dosed every 12 hours

Insulin Aspart

Brand Names
NovoLog, NovoLog FlexPen, NovoLog FlexTouch

Generic Name
Insulin aspart (rapid-acting insulin)

Rx Only

Dosage Forms
Injection 100 units/ml (10 ml vial and 3 ml cartridge for pen use)

Pregnancy Category B

Dosing

- Administer SUB-Q 15 minutes before or immediately after starting a meal
- May be administered by continuous subcutaneous infusion (insulin pump)

◉ 70% Intermediate-Acting Insulin Aspart Suspension and 30% Rapid-Acting Aspart Solution

Brand Name

NovoLog Mix 70/30

Generic Name

70% Intermediate-Acting Insulin Aspart Suspension and 30% Rapid-Acting Aspart Solution

Rx Only

Dosage Forms

Injection 100 units/ml (10 ml vial and 3 ml cartridge for pen use)

Pregnancy Category B

Comparison of Insulin Products

Refer to **Table 2-1**.

TABLE 2–1 Comparison of Insulin Products

Product	Onset (Hours)	Peak (Hours)	Duration (Hours)	Appearance
Rapid-Acting Insulin				
Insulin aspart (NovoLog)	0.25	1–2	3–5	Clear
Insulin glulisine (Apidra)	0.25	1	3–4	Clear
Insulin lispro (Humalog)	0.25	0.5–1.5	3–4	Clear
Insulin Inhalation (Afrezza)	0.25	1	3	Powder
Short-Acting Insulin				
Regular Insulin (Humulin R, Novolin R)	0.5–1	2–3	3–6	Clear
Intermediate-Acting Insulin				
NPH insulin (Humulin N, Novolin N)	2–4	6–10	10–16	Cloudy
Long-Acting Insulin				
Insulin detemir (Levemir)	4	N/A	12–24	Clear
Insulin glargine (Basaglar, Lantus, Toujeo)	4	N/A	24	Clear

SODIUM-GLUCOSE COTRANSPORTER 2 (SGLT-2) INHIBITORS

Introduction

The sodium-glucose cotransporter 2 (SGLT-2) inhibitors decrease plasma glucose by increasing urinary excretion of glucose. They are used as adjuncts to diet and exercise in patients with type 2 diabetes mellitus. Recent clinical data suggest that patients taking empagliflozin demonstrated a reduction in the risk of cardiovascular death. Average HbA1c reductions are between 0.7% and 1%.

Mechanism of Action for the Drug Class

Sodium-glucose Cotransporter 2 (SGLT-2) inhibitors reduce reabsorption of filtered glucose from the proximal tubular lumen and decreases the renal threshold for glucose, thereby reducing plasma glucose concentrations

Usage for the Drug Class

Type 2 diabetes mellitus

Adverse Reactions for the Drug Class: Most Common

Hypoglycemia (when used with other oral antidiabetic drugs that may cause hypoglycemia), urinary tract infection, increased urine output, increased LDL cholesterol, nausea, genitourinary fungal infections

Adverse Reactions for the Drug Class: Rare/Severe/Important

Increased serum creatinine, hypotension, ketoacidosis, urosepsis

Major Drug Interactions for the Drug Class

Drugs Affecting SGLT-2 Inhibitors

Thiazides and Thiazide-like diuretics: Decreased efficacy

SGLT-2 Inhibitors' Effects on Other Drugs

Loop diuretics: Increased risk for hypotension

Contraindications for the Drug Class

GFR < 30 ml/min, ESRD, hemodialysis

Essential Monitoring Parameters for the Drug Class

HbA1c at least twice a year, serum glucose, renal function

Key Points

- **Black Box Warnings:**
  - Increased risk of bone mineral loss and bone fractures
  - Increased risk of acute kidney injury

Members of the Drug Class

In this section: Canagliflozin, Dapagliflozin, Empagliflozin

Canagliflozin

Brand Name

Invokana

Generic Name

Canagliflozin

Rx Only

Dosage Form

Tablet

Pregnancy Category C

Dosing

- Initial dose: 100 mg once daily prior to the first meal of the day
- Maximum recommended dose: 300 mg once daily in patients with GFR > 60 ml/min
- Renal dosage adjustment:
  - GFR 45 ml/min to < 60 ml/min: Maximum 100 mg once daily
  - GFR ≥ 30 ml/min to 45 ml/min: Not recommended for initiation of therapy
  - GFR < 30 ml/min: Use is contraindicated

Dapagliflozin

Brand Name

Farxiga

Generic Name

Dapagliflozin

Rx Only

Dosage Form

Tablet

Pregnancy Category C

Dosing

- Initial dose: 5 mg once daily
- Maximum recommended dose: 10 mg once daily
- Renal dosage adjustment:
  - GFR 30–60 ml/min: Drug is not recommended
  - GFR < 30 ml/min: Use is contraindicated

Empagliflozin

Brand Name

Jardiance

Generic Name

Empagliflozin

Rx Only

Dosage Form

Tablet

Pregnancy Category: (Not recommended During Second or Third Trimester)

Dosing

- Initial dose: 10 mg once daily
- Maximum recommended dose is 25 mg once daily
- Renal dosage adjustment:
  - GFR 30 ml/min to ≤ 45 ml/min: Not recommended for initiation of therapy
  - GFR < 30 ml/min: Use is contraindicated

SULFONYLUREAS

Introduction

The sulfonylureas are used as adjunctive therapy to diet and exercise in patients with type 2 diabetes mellitus. Although periodically used as monotherapy, sulfonylureas are more commonly used in combination with other oral antidiabetic agents, sometimes in the same formulation, in patients who do not reach glycemic goals. General dosing guidelines are to start with a low dose and titrate upward according to patient response while monitoring for signs and symptoms of hypoglycemia, which is a common adverse effect

of the drug class. Those drugs should be used cautiously in patients with renal or hepatic impairment. Average HbA1c reductions are between 1% and 2%.

Mechanism of Action for the Drug Class

Lowers blood glucose by stimulating insulin release from the beta cells of the pancreatic islets

Usage for the Drug Class

Type 2 diabetes mellitus

Pregnancy Category C for the Drug Class

Exception: glyburide (pregnancy category B)

Adverse Reactions for the Drug Class: Most Common

Hypoglycemia, GI distress, dizziness

Adverse Reactions for the Drug Class: Rare/Severe/Important

SIADH (most commonly with chlorpropamide); disulfiram-like reactions

Major Drug Interactions for the Drug Class

Drugs Affecting Sulfonylureas

- Anticoagulants, azole antifungals, gemfibrozil-enhanced hypoglycemic effects
- Beta blockers cause decreased hypoglycemic effects; also, may mask signs and symptoms of hypoglycemia

Sulfonylureas' Effects on Other Drugs

- Digoxin: Increased levels

Contraindications for the Drug Class

Diabetes complicated by ketoacidosis, with or without coma; Type 1 diabetes mellitus; diabetes complicated by pregnancy

Essential Monitoring Parameters for the Drug Class

HbA1c at least twice a year, serum glucose, renal function

Counseling Point for the Drug Class

Monitor glucose as directed and be aware of the signs and symptoms of hypoglycemia

Members of the Drug Class

In this section: Glimepiride, glipizide, glyburide
Others: Chlorpropamide, tolazamide, tolbutamide

Glimepiride

Brand Name

Amaryl

Generic Name

Glimepiride

Rx Only

Dosage Form

Tablet

Dosing

- Initial dose: 1–2 mg once daily at breakfast
- Maintenance dose: 1–8 mg once daily

Glipizide

Brand Names

Glucotrol, Glucotrol XL

Generic Names

Glipizide, glipizide extended-release

Rx Only

Dosage Forms

Tablet, extended-release tablet

Dosing

- Initial dose:
  - Glucotrol: 2.5–5 mg once daily 30 minutes before breakfast
  - Glucotrol XL: 5 mg extended-release once daily with breakfast
- Maintenance dose:
  - Glucotrol: 10–40 mg daily (> 15 mg/day should be divided)
  - Glucotrol XL: 5–20 mg extended-release once daily

Glyburide

Brand Names

DiaBeta, Micronase, Glynase PresTab

Generic Name

Glyburide

Rx Only

Dosage Form

Tablet

Dosing

DiaBeta and Micronase

- Initial dose: 1.25–5 mg once daily with breakfast
- Maintenance dose: 1.25–20 mg once daily; may give as single or divided doses

Glynase PresTab

- Initial dose: 1.5–3 mg once daily with breakfast
- Maintenance dose: 1.5–12 mg once daily; may give as single or divided doses

THIAZOLIDINEDIONES

Introduction

The thiazolidinediones decrease insulin resistance by enhancing insulin-receptor sensitivity. They are used as adjuncts to diet and exercise in patients with type 2 diabetes mellitus. Although periodically used as monotherapy, thiazolidinediones are more frequently used in combination with other oral antidiabetic agents in patients who do not reach glycemic goals. Clinical data suggest that patients taking thiazolidinediones may be at an increased risk of myocardial infarction and death; thus, they should be used with caution in patients with a history of previous cardiac disease. They are contraindicated in patients with NYHA class III or IV heart failure. A structurally similar thiazolidinedione, troglitazone, was removed from the market due to cases of liver failure and death. The current agents are recommended to avoid use in patients with hepatic dysfunction. Average HbA1c reductions are between 1% and 1.5%.

Mechanism of Action for the Drug Class

Thiazolidinediones increase insulin sensitivity by affecting the peroxisome proliferator-activated receptor gamma (PPAR-γ). Acting as an agonist to this receptor, thiazolidinediones decrease insulin resistance in adipose tissue, skeletal muscle, and the liver.

Usage for the Drug Class

Type 2 diabetes mellitus

Adverse Reactions for the Drug Class: Most Common

Weight gain, edema, hypoglycemia (when used with other oral antidiabetic drugs that may cause hypoglycemia)

Adverse Reactions for the Drug Class: Rare/Severe/Important

Hepatic failure, heart failure, anemia, ovulation in anovulatory premenopausal women, bone loss, bladder cancer, macular edema

Major Drug Interactions for the Drug Class

Drugs Affecting Thiazolidinediones

- Gemfibrozil: Increased levels
- Rifampin: Decreased levels

Thiazolidinediones' Effects on Other Drugs

- Oral contraceptives: Decreased efficacy

Contraindications for the Drug Class

Patients with NYHA class III and IV heart failure; active liver disease (alanine aminotransferase [ALT] > 2.5 times the upper limit of normal)

Essential Monitoring Parameters for the Drug Class

HbA1c at least twice a year, serum glucose, liver function

Key Points

- **Black Box Warnings:**
  - Can exacerbate congestive heart failure in some patients.
  - May be linked to an increased risk of bladder cancer

Counseling Point for the Drug Class

- Report signs and symptoms of liver dysfunction and/or shortness of breath immediately

Members of the Drug Class

In this section: Pioglitazone
Others: Rosiglitazone

◉ Pioglitazone

Brand Name

Actos

Generic Name

Pioglitazone

Rx Only

Dosage Form

Tablet

Pregnancy Category C

Dosing

- Initial dose:
  - 15–30 mg once daily without regard to meals
  - Limit initial dose to 15 mg once daily in patients with NYHA class I and II heart failure
- Maintenance dose:
  - 15–45 mg once daily
- Maximum recommended dose: 15 mg once daily in patients taking strong CYP2C8 inhibitors (e.g., gemfibrozil)

REVIEW QUESTIONS

1. Which of the following medications has a warning about a rare but serious metabolic complication called lactic acidosis?
   a. Sitagliptin
   b. Metformin
   c. Exenatide
   d. Pioglitazone

2. What is the maximum daily dose of immediate-release metformin?
   a. 1000 mg
   b. 1500 mg
   c. 2000 mg
   d. 2550 mg

3. A patient's GFR is 20 ml/min; what is the starting dose of metformin?
   a. 500 mg BID
   b. 1000 mg BID
   c. 2000 mg once daily
   d. Use is contraindicated

4. What is the mechanism of action of dapagliflozin?
   a. Inhibits di-peptidyl peptidase-4
   b. Inhibits sodium-glucose Cotransporter-2
   c. Acts as a direct GLP-1 agonist
   d. Stimulates insulin release from the pancreas

5. Which of the following is a brand name of exenatide?
   a. Farxiga
   b. Jardiance
   c. Bydureon
   d. Victoza

6. Which class of drugs may cause decreased bone mineral density and bone fractures?
   a. Biguanide
   b. GLP-1 agonist
   c. SGLT-2 inhibitor
   d. Sulfonylurea

7. Which of the following drugs can be used in a patient with a GFR of < 30 ml/min?
   a. Liraglutide
   b. Exenatide
   c. Metformin
   d. Canagliflozin

8. Acute pancreatitis has been reported with which of the following drugs?
   a. Sitagliptin
   b. Metformin
   c. Basaglar insulin
   d. Glipizide XL

9. Which of the following is a proper counseling point for a patient taking metformin?
   a. Temporarily withhold in patients undergoing radiologic procedures involving iodinated contrast
   b. Use proper SUB-Q injection technique
   c. Monitor for urinary tract infections
   d. Monitor for signs and symptoms of acute pancreatitis

10. Before initiating, which of the following should you perform spirometry (FEV1)?
    a. Liraglutide
    b. Basaglar insulin
    c. Exenatide
    d. Afrezza

11. What is the typical starting dose of empagliflozin?
    a. 5 mg
    b. 10 mg
    c. 25 mg
    d. 100 mg

12. Which of the following is NOT a brand name for insulin glargine?
    a. Toujeo
    b. Lantus
    c. Apidra
    d. Basaglar

13. Which of the following is the average HbA1c reduction with sulfonylureas?
    a. 0.7–1%
    b. 1–1.5%
    c. 1–2 %
    d. 1.5–2%

14. Which of the following medications can be dosed once weekly?
    a. Lantus
    b. Toujeo
    c. Afrezza
    d. Victoza

15. What is the correct dose of sitagliptin in a patient with a GFR of 40 ml/min?
    a. 100 mg
    b. 50 mg
    c. 25 mg
    d. Use is contraindicated

16. Inhibition of di-peptidyl peptidase-4 is the mechanism of action of which drug?
    a. Glimepiride
    b. Metformin
    c. Insulin
    d. Sitagliptin

17. Insulin inhalation powder is most closely related to which insulin?

- **a.** Aspart
- **b.** Regular
- **c.** NPH
- **d.** Detemir

18. All of the following are counseling points regarding insulin EXCEPT

- **a.** Rotate injection sites to prevent lipodystrophy
- **b.** Wear diabetic identification
- **c.** Mild episodes of hypoglycemia should be treated with glucagon
- **d.** Insulin stored at room temperature will be less painful

19. All of the following are rapid-acting insulins EXCEPT

- **a.** Lispro
- **b.** Glulisine
- **c.** Aspart
- **d.** Detemir

20. Which of the following has been used to treat antipsychotic-induced weight gain?

- **a.** Glyburide
- **b.** Pioglitazone
- **c.** Metformin
- **d.** NPH insulin

21. Which class of drugs has rare but serious side effects of arthralgia, bullous pemphigoid, and Stevens-Johnson syndrome?

- **a.** Biguanide
- **b.** Sulfonylurea
- **c.** DPP-4 inhibitor
- **d.** SGLT-2 inhibitor

22. Which drug needs to be avoided in a patient with a personal or family history of medullary thyroid carcinoma?

- **a.** Canagliflozin
- **b.** Glipizide
- **c.** Exenatide
- **d.** Pioglitazone

23. When a patient is stable on a current dose of insulin, how often should you check the HbA1c?

- **a.** Weekly
- **b.** Monthly
- **c.** Every 6 months
- **d.** Every 2 years

24. Hypoglycemia, cough, and throat irritation are side effects of which of the following?

- **a.** Afrezza
- **b.** Apidra
- **c.** Humalog
- **d.** NovoLog

25. Which insulin is commercially available in 200 units/ml?

- **a.** Aspart
- **b.** Lispro
- **c.** Glargine
- **d.** Detemir

26. Which class of drugs has a rare but serious side effect of causing ketoacidosis?

- **a.** SGLT-2 inhibitor
- **b.** GLP-1 agonist
- **c.** Biguanide
- **d.** Insulin

27. What is the maximum recommended dose of Invokana in a patient with a GFR of 80 ml/min?

- **a.** 50 mg
- **b.** 100 mg
- **c.** 250 mg
- **d.** 300 mg

28. Humalog Mix 75/25 contains which of the following?

- **a.** 75% rapid-acting lispro and 25% intermediate-acting lispro suspension
- **b.** 25% rapid-acting lispro and 75% intermediate-acting lispro suspension
- **c.** 75% regular insulin and 25% NPH insulin
- **d.** 25% regular insulin and 75% NPH insulin

29. Toujeo is available in which of the following concentrations?

- **a.** 100 units/ml
- **b.** 300 units/ml
- **c.** 500 units/ml
- **d.** Both a and b are correct

30. Which of the following statements regarding Bydureon is FALSE?

- **a.** It is a GLP-1 agonist
- **b.** It is administered as a SUB-Q injection
- **c.** It is dosed twice daily
- **d.** It has a rare but serious side effect of acute pancreatitis

CHAPTER 3

Anti-Infective Agents

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AMINOGLYCOSIDES

Introduction

Aminoglycosides are bactericidal, Gram-negative agents that are used systemically to treat serious infections. They are notable for their toxicities, namely nephrotoxicity and ototoxicity. They often are used empirically and then the patient is transitioned to safer agents as culture results become available. Gentamicin and tobramycin are extremely similar drugs, with virtually identical pharmacokinetics and dosing. Only minor differences in spectra separate them. Neomycin is combined with polymyxin B and used topically for superficial infections.

Mechanism of Action for the Drug Class

Aminoglycosides irreversibly bind to the 30S ribosomal subunit, disrupting bacterial protein synthesis, and resulting in cell death.

Members of the Drug Class

In this section: Gentamicin, tobramycin, neomycin-polymyxin B
Others: Amikacin, streptomycin

⦿ Gentamicin

Brand Name

Garamycin

Generic Name

Gentamicin

Rx Only

Dosage Form

Injection

Usage

Systemic aerobic Gram-negative infections of the bloodstream, lung, skin and soft tissue, bone, CNS, abdomen, heart, including those caused by Pseudomonas aeruginosa; systemic infections (in particular, those of the bloodstream and/or heart) caused by staphylococci, streptococci, or enterococci (treatment must be in combination with a cell-wall active agent for Gram-positive infections)

Pregnancy Category D

Dosing

- Initial dose:
  - Conventional dosing: 1.5–2 mg/kg per dose every 8 hours based on ideal or adjusted body weight
  - Extended-interval dosing: 5–7 mg/kg per day based on ideal or adjusted body weight
- Renal dosage adjustment: Dosing must be individualized based on CrCl and therapeutic drug monitoring

Pharmacokinetic Monitoring

Peaks associated with efficacy range from 5–10 µg/ml, with higher concentrations for more severe or resistant infections. Troughs associated with decreased nephrotoxicity range from < 1–2 µg/ml. Extended-interval dosing is monitored via nomograms with concentrations measured 6 to 14 hours from the time of administration. Do not use traditional peak and trough concentrations to monitor aminoglycosides dosed this way.

Adverse Reactions: Most Common

Electrolyte wasting (particularly potassium and magnesium); nephrotoxicity, manifesting usually as increased serum creatinine before changes in urine output are seen

Adverse Reactions: Rare/Severe/Important

Ototoxicity; neuromuscular blockade

Major Drug Interactions

Drugs Affecting Gentamicin

Concomitant oto- or nephrotoxic agents: Additive oto- or nephrotoxicity

Gentamicin's Effect on Other Drugs

Neuromuscular blocking agents: Potentiated neuromuscular blockade

Essential Monitoring Parameters

Peaks and troughs should be monitored, particularly during extended therapy. If extended-interval dosing is used, gentamicin concentrations should be monitored and measured by a nomogram. Patients should be monitored and examined for hearing and balance changers.

Counseling Point

Report any changes in hearing function or decline in urination to a healthcare practitioner immediately

Key Points

- Monitor serum peak and trough levels to ensure nontoxic levels. Nephrotoxicity is more likely with elevated trough concentrations, but toxicities can occur at any concentration.
- Ototoxicity is irreversible. Patients receiving extended courses of aminoglycosides must have their hearing monitored. Aminoglycosides should be discontinued at the first sign of hearing or balance problems.
- Extended-interval dosing may be more effective and less nephrotoxic than traditional dosing. However, it is not ideal for patients with changing renal function.
- Dosage should be based on ideal or adjusted body weight, not total body weight

◉ Tobramycin

Brand Names

Tobrex, Tobi (inhalation)

Generic Name

Tobramycin

Rx Only

Dosage Forms

Injection, inhalation

Usage

- IV: Same as gentamicin
- Inhalation: Given to improve pulmonary function in cystic fibrosis by decreasing bacterial colony counts

Pregnancy Category D

Dosing

- IV: Same as gentamicin
- Inhalation: 300 mg every 12 hours

Essential Monitoring Parameters

Peaks and troughs should be monitored, particularly during extended therapy. If extended-interval dosing is used, tobramycin concentrations should be monitored and measured by a nomogram.

Key Points

- All the preceding points for gentamicin apply to tobramycin. Tobramycin has slightly better activity against *Pseudomonas aeruginosa* than gentamicin, and gentamicin has slightly better activity against Gram-positive organisms and *Klebsiella pneumoniae* than tobramycin, but they are otherwise very similar.
- Inhalation therapy with tobramycin is used to prevent exacerbations in cystic fibrosis patients. It should not be used as monotherapy to treat pneumonia.

◉ Neomycin-Polymyxin B

Brand Name

Neosporin

Generic Name

Neomycin-polymyxin B

OTC

Dosage Forms

Topical ointment or cream

Usage

Minor skin infections

Pregnancy Category C

Dosing

Apply to affected area 3 to 4 times daily

Adverse Reactions: Most Common

Local irritation

Counseling Points

- Do not use for deep wounds, puncture wounds, animal or human bites, or serious burns
- Do not apply to the eyes
- Cover treated area with a gauze or bandage
- See a healthcare provider if the wound does not begin to heal in a few days

Key Points

- Neomycin is an aminoglycoside antibiotic. It is often coupled with polymyxin B in a topical formulation with the brand name Neosporin. Note that not all products that contain the Neosporin name contain the neomycin/polymyxin B combination.
- Topical antibiotics are not effective in the treatment of skin infections that are any more severe than superficial

CEPHALOSPORINS

Introduction

Cephalosporins are beta-lactam antibiotics and the largest class of antibiotics. They are more resistant to beta-lactamase enzymes (enzymes produced by bacteria to destroy beta-lactams) than penicillins, although beta-lactamases that destroy cephalosporins have since evolved. They have more broad-spectrum antimicrobial activity than penicillins, activity that broadens in spectrum, moving "through" the generations from first- to fourth-generation agents. The cephalosporins listed here are among the most frequently used and are representative of the much larger category of drugs.

- **First-generation:** cefadroxil, cefazolin, cephalexin, cephalothin, cephapirin
- **Second-generation:** cefaclor, cefamandole, cefonicid, ceforanide, cefoxitin, cefotetan, cefprozil, cefuroxime, loracarbef, moxalactam
- **Third-generation**: cefdinir, cefixime, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone
- **Fourth-generation**: cefepime
- **Anti-MRSA cephalosporin**: ceftaroline
- **Cephalosporin combinations**: ceftazidime/avibactam, ceftolozane/tazobactam

Mechanism of Action for the Drug Class

Inhibit bacterial cell growth in susceptible bacteria by inhibiting transpeptidase enzymes (also known as penicillin-binding proteins). This prevents the cross-linking of peptidoglycan strands, thereby inhibiting the synthesis of the bacterial cell wall.

Adverse Reactions for the Drug Class: Most Common

Hypersensitivity, rash, diarrhea

Adverse Reactions for the Drug Class: Rare/Severe/Important

Anaphylaxis, bone marrow suppression, *Clostridium difficile*-associated diarrhea

Counseling Point for the Drug Class

Report any signs of an allergic reaction, such as a rash or hives, to your healthcare provider immediately

Key Point for the Drug Class

Use with caution in patients who are allergic to penicillin derivatives. Cross-reactivity between the two types of beta-lactams seems to be lower than initially suggested but is still possible.

Members of the Drug Class

In this section: Cefprozil, cefdinir, ceftriaxone, cefuroxime, cephalexin, cefepime

Others: Cefaclor, cefadroxil, cefamandole, cefazolin, cefixime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefoxitin, cefprozil, ceftazidime, ceftazidime/avibactam, ceftibuten, ceftizoxime, ceftolozane/tazobactam, cephalexin, cephalothin, cephapirin, loracarbef, moxalactam

Cefprozil

Brand Name

Cefzil

Generic Name

Cefprozil

Rx Only

Dosage Forms

Tablet, suspension

Usage

Upper and lower respiratory tract infections, uncomplicated skin and skin structure infections, tonsillitis

Pregnancy Category B

Dosing

- Adults: 250–500 mg twice daily
- Pediatrics: 7.5 mg/kg twice daily or 20 mg/kg daily, depending on the indication
- Renal dosage adjustment: Reduce dose by 50% with a creatinine clearance of < 30 ml/min

Adverse Reactions: Most Common

Nausea, vomiting

Major Drug Interactions

Drugs Affecting Cefprozil

Probenecid: Increases concentrations of cefprozil through impaired excretion

Key Points

- The oral suspension contains phenylalanine and should be avoided in patients with phenylketonuria
- This is a second-generation cephalosporin

Cefdinir

Brand Name

Omnicef

Generic Name

Cefdinir

Rx Only

Dosage Forms
Capsule, suspension

Usage
Upper and lower respiratory infections, uncomplicated skin and skin-structure infections

Pregnancy Category B

Dosing
- Adults: most indications 300 mg twice daily or 600 mg once daily
- Pediatrics: 7 mg/kg/dose twice daily or 14 mg/kg/dose once daily
- Renal dosage adjustment: If CrCl < 30 ml/min, then 300 mg once daily

Key Point
- Cefdinir is a third-generation cephalosporin

Ceftriaxone
Brand Name
Rocephin

Generic Name
Ceftriaxone

Rx Only

Dosage Forms
Injection (IV and IM)

Usage
Upper and lower respiratory tract infections, skin and skin-structure infections, *urinary tract infections, gonorrhea*, pelvic inflammatory disease, bacteremia, endocarditis, bone and joint infections, intra-abdominal infections, *meningitis*, surgical prophylaxis, *Lyme disease*

Pregnancy Category B

Dosing
- Adults:
  - Most indications: 1–2 g given once daily; maximum daily dose not to exceed 4 g
  - Meningitis: 2 g IV every 12 hours
  - Gonorrhea: 250 mg IM given once
- Pediatrics:
  - Mild to moderate infections: 50–75 mg/kg given daily (in one or two divided doses); maximum daily dose should not exceed 2 g
  - Meningitis: 100 mg/kg daily (in one to two divided doses); maximum daily dose should not exceed 4 g

Adverse Reactions: Most Common
Injection-site irritation; biliary sludging in neonates

Key Points
- In patients receiving long-term therapy, ceftriaxone-calcium may deposit in the gallbladder. This has been associated with symptoms of gallbladder disease. This salt deposition and subsequent symptoms are reversible upon discontinuation of ceftriaxone therapy.
- In neonates, calcium and ceftriaxone can form complexes that deposit in lung and kidney tissue and may be fatal. Alternative cephalosporins should be used.
- Biliary sludging may lead to jaundice in neonates. Alternative cephalosporins should be used in neonates.
- This is a third-generation cephalosporin
- Patients being treated for gonorrhea should receive concomitant therapy for chlamydia

Cefuroxime
Brand Name
Ceftin

Generic Name
Cefuroxime

Rx Only

Dosage Forms
Tablet, suspension, injection

Usage
Upper and lower respiratory tract infections, uncomplicated skin and skin-structure infections, urinary tract infections, tonsillitis, Lyme disease

Pregnancy Category B

Dosing
- Adults: 250–500 mg twice daily
- Pediatrics (younger than 12 years): 20–30 mg/kg per day divided into two doses (maximum daily dose: 1 g)
- Renal dosage adjustment: Dose every 24 hours with a CrCl of < 30 ml/min

Key Points
- Available both intravenously and orally, unlike many beta-lactam antibiotics
- This is a second-generation cephalosporin and has a similar antimicrobial spectrum to cefprozil
- No longer recommended for gonorrhea because of resistance

Cephalexin
Brand Names
Keflex, Keftab

Generic Name
Cephalexin

Rx Only

Dosage Forms
Capsule, tablet, suspension

Usage
Upper respiratory tract infections, *uncomplicated skin and soft-tissue infections*, urinary tract infections

Pregnancy Category B

Dosing
- Adults: 1–4 g daily in divided doses; most commonly 250 mg 4 times daily
- Pediatrics: 25–100 mg/kg per day in 2 to 4 divided doses (maximum daily dose: 4 g)
  - Acute otitis media, 75–100 mg/kg per day in 4 divided doses
- Renal dosage adjustment: Adjust for CrCl < 60 ml/min

Key Points
- Most commonly used for skin infections, but it is ineffective against methicillin-resistant *Staphylococcus aureus* (MRSA). Cephalexin remains highly active against streptococci that cause skin infections.
- This is a first-generation cephalosporin

Cefepime

Brand Names
Maxipime

Generic Name
Cefepime

Rx Only

Dosage Forms
Injection

Usage
Lower respiratory tract infections, skin and soft-tissue infections, urinary tract infections, *febrile neutropenia,* bone and joint infection, meningitis

Pregnancy Category B

Dosing
- Adults: 2 g every 8 to 12 hours
- Pediatrics: 50 mg/kg/dose every 8 to 12 hours (maximum of 2 g/dose)
- Renal dosage adjustment: Adjust for CrCl < 60 ml/min

Adverse Reactions: Rare/Severe/Important
Nonconvulsive encephalopathy

Key Points
- Cefepime is a broad-spectrum antibiotic and is active against *Pseudomonas aeruginosa*; however, it does not have useful activity against anaerobes and if anaerobic coverage is needed and another antibiotic, such as metronidazole, needs to be given in addition.
- This is a fourth-generation cephalosporin

CYCLIC LIPOPEPTIDES

Introduction
Daptomycin is the only currently available cyclic lipopeptide. It is an IV-only agent with potent bactericidal therapy against many Gram-positive bacteria, including strains of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci. Resistance to daptomycin is currently low but has been reported in staphylococci and enterococci.

Mechanism of Action for the Drug Class
Daptomycin inserts itself into the cell membrane of Gram-positive bacteria through a calcium-dependent process, leading to holes in the membrane that leak essential intra-cellular cations and cell death.

Members of the Drug Class
In this section: Daptomycin

Daptomycin

Brand Name
Cubicin

Generic Name
Daptomycin

Rx Only

Dosage Form
Injection

Usage
Skin and skin-structure infections, *bacteremia, endocarditis*, urinary tract infections, prosthetic joint infection

Pregnancy Category B

Dosing

- Skin and skin-structure infections: 4 mg/kg daily
- Bacteremia and endocarditis: 6 mg/kg daily
- Higher doses of 8–10 mg/kg daily are recommended by some experts in cases of complicated methicillin-resistant *Staphylococcus aureus* bacteremia and endocarditis
- Renal dosage adjustment: If CrCl < 30 ml/min, administer every other day

Adverse Reactions: Most Common

Myopathy, CPK elevation

Adverse Reactions: Rare/Severe/Important

Eosinophilic pneumonia, rhabdomyolysis

Major Drug Interactions

Drugs Affecting Daptomycin

HMG-CoA reductase inhibitors: Increased risk of CPK elevations, myopathy

Counseling Points

- Report any muscle pain or changes in urine color immediately
- If you are administering this drug yourself at home, do not double doses if a day of drug is missed. This can increase the risk of muscle toxicity.

Key Points

- Daptomycin is useful in that it is active against both methicillin-resistant *S. aureus* and vancomycin-resistant enterococci, but resistance to it does occur rarely. Verify susceptibility through testing.
- Daptomycin distributes to the lungs, but it is inactivated by pulmonary surfactant and cannot be used for the treatment of respiratory infections such as pneumonia
- Daptomycin can be given both by IV infusion and IV push, which can be convenient for outpatient infusion centers

FLUOROQUINOLONES

Introduction

Fluoroquinolones are among the most frequently used antibiotics. Their use is driven by their relatively broad antimicrobial spectra and their once- or twice-daily dosing schedules. All are available both intravenously and orally, making transitional therapy easy in the inpatient setting. Unfortunately, frequent use of fluoroquinolones has led to inevitable increases in antimicrobial resistance, particularly in *P. aeruginosa, E. coli*, and *Neisseria gonorrhea*.

Mechanism of Action for the Drug Class

Fluoroquinolones inhibit DNA gyrase (topoisomerase II) and topoisomerase IV, which interferes with bacterial DNA coiling, which kills the organism

Pregnancy Category C for the Drug Class

Adverse Reactions for the Drug Class: Most Common

Headache, dizziness, confusion, photosensitivity, nausea, diarrhea

Adverse Reactions for the Drug Class: Rare/Severe/Important

QTc prolongation, hypotension, tremor, seizures, skin reactions, hepatitis, acute interstitial nephritis, arthropathy, tendinopathy, tendon rupture (Achilles tendon), hypoglycemia, pseudomembranous colitis

Major Drug Interactions for the Drug Class

Drugs Affecting Fluoroquinolones

Di- and trivalent cations: Greatly decrease oral fluoroquinolone absorption

Fluoroquinolones' Effects on Other Drugs

QTc-prolonging drugs: Potentiated QTc prolongation, possibly leading to polymorphic ventricular tachycardia

Counseling Points for the Drug Class

- Complete the full prescribed course of therapy
- Separate administration from di- and trivalent cations by at least 2 hours
- Avoid excessive exposure to sunlight; use sunscreen if exposure is unavoidable

Key Points for the Drug Class

- **Black Box Warning:**
  - Fluoroquinolones have been associated with tendinitis, tendon rupture, peripheral neuropathy, and CNS effects. Fluoroquinolones may exacerbate myasthenia gravis and should be avoided in patients with a known history of myasthenia gravis.
- The safety and efficacy of fluoroquinolones in children < 18 years of age (except for the use of ciprofloxacin following exposure to inhalational anthrax and in children with cystic fibrosis), pregnant women, and lactating women has not been established. They are generally avoided in those populations for that reason.

Members of the Drug Class

In this section: Ciprofloxacin, levofloxacin, moxifloxacin
Others: Gemifloxacin, ofloxacin

Ciprofloxacin

Brand Names

Cipro, Cipro XR

Generic Name

Ciprofloxacin

Rx Only

Dosage Forms

Tablet, extended-release tablet, suspension, injection, ophthalmic solution, and ointment, otic suspension

Usage

Upper and lower respiratory tract infections, urinary tract infections, intra-abdominal infections, skin and soft-tissue infections, bone and joint infections, infectious diarrhea, anthrax

Dosing

- Oral: 250–750 mg twice daily dependent on the location and severity of infection
- Oral extended-release: 500–1000 mg daily for urinary tract infections
- IV: 200–400 mg twice or three times daily dependent on the location and severity of infection
- Renal dosage adjustment: Required with CrCl of < 30–50 ml/min

Major Drug Interactions

Drugs Affecting Ciprofloxacin

NSAIDs: May increase the risk of CNS stimulation and/or seizures

Ciprofloxacin's Effect on Other Drugs

- Theophylline: Concentrations increase by 33% on average, but may be much higher
- Phenytoin: Both increased and decreased levels have been reported; close monitoring is recommended
- Warfarin: Enhanced anticoagulant effect

Key Points

- Ciprofloxacin has less Gram-positive activity than other fluoroquinolones, and treatment failures have been reported in streptococcal pneumonia. It is better used in hospital-acquired pneumonia than community-acquired pneumonia.
- Ciprofloxacin is one of two fluoroquinolones with clinically useful activity against *P. aeruginosa*, although resistance to it is high in many hospitals
- Resistance in *N. gonorrhea* to fluoroquinolones has risen to the point that they are no longer recommended in the treatment of gonorrhea

Levofloxacin

Brand Name

Levaquin

Generic Name

Levofloxacin

Rx Only

Dosage Forms

Tablet, injection, ophthalmic solution

Usage

Upper and lower respiratory tract infections, urinary tract infections, skin and soft-tissue infections, intra-abdominal infections

Dosing

- 250–750 mg once daily, depending on indication
- Renal dosage adjustment: See **Table 3-1**

Major Drug Interactions

Drugs Affecting Levofloxacin

NSAIDs: May increase the risk of CNS stimulation and/or seizures

Levofloxacin's Effect on Other Drugs

Antidiabetic agents: May result in enhanced hypoglycemic effect

Key Points

- Levofloxacin has strong Gram-negative and Gram-positive activity, and it is useful in both hospital- and community-acquired infections such as pneumonia
- Levofloxacin is one of two fluoroquinolones with clinically useful activity against *P. aeruginosa*, although resistance to it is high in many hospitals
- Some indications for levofloxacin use higher dosing to shorten the course of therapy (e.g., community-acquired pneumonia)
- Levofloxacin has excellent absorption and is given in equivalent doses orally and intravenously

TABLE 3–1 Renal Dosage Adjustment for Levofloxacin

Dose with Normal Renal Function	CrCl 20–49 ml/min	CrCl 10–19 ml/min
750 mg daily	750 mg every 48 hours	750 mg × 1, then 500 mg every 48 hours
500 mg daily	500 mg × 1, then 250 mg every 24 hours	500 mg × 1, then 250 mg every 48 hours
250 mg daily	250 mg daily	250 mg every 48 hours

◉ Moxifloxacin

Brand Name
Avelox

Generic Name
Moxifloxacin

Rx Only

Dosage Forms
Tablet, injection

Usage
Upper and lower respiratory tract infections, skin and soft-tissue infections, intra-abdominal infections

Dosing
- 400 mg once daily
- No renal dose adjustment is necessary

Key Points
- Unlike most other fluoroquinolones (including the two listed here), moxifloxacin is not eliminated by the kidney but is instead excreted via the biliary tract. For this reason, it is not used in the treatment of urinary tract infections.
- Moxifloxacin has potent activity against many Gram-positive organisms and has more activity against anaerobic bacteria than other fluoroquinolones. However, resistance among anaerobes rose quickly and it should not be used as monotherapy for many intra-abdominal infections.
- Moxifloxacin lacks activity against *P. aeruginosa* and is more suitable for therapy for community-acquired pneumonia than hospital-acquired pneumonia

FOLIC ACID SYNTHESIS INHIBITORS

Introduction
The folic acid synthesis inhibitors, trimethoprim and the sulfonamides, work synergistically to prevent bacterial growth and replication. The sulfonamides were the first antibiotics made available and introduced the antibiotic era. They are still used today, most commonly in trimethoprim/sulfamethoxazole, where the two active ingredients work together in susceptible bacteria.

Mechanism of Action for the Drug Class
Trimethoprim inhibits folate utilization by inhibiting dihydrofolate reductase in bacteria. Sulfamethoxazole and other sulfonamides compete with para-aminobenzoic acid (PABA) in an earlier step in folate synthesis that only exists in bacteria. The two types of drugs have synergistic activity in many bacteria.

Members of the Drug Class
In this section: Trimethoprim/sulfamethoxazole
Others: Sulfadiazine, sulfisoxazole; topical formulations

◉ Trimethoprim/Sulfamethoxazole

Brand Names
Bactrim, Septra

Generic Name
Trimethoprim/sulfamethoxazole

Rx Only

Dosage Forms
Tablet, suspension, injection

Usage
Urinary tract infections, upper and lower respiratory tract infections, skin and skin-structure infections, treatment, and prophylaxis of Pneumocystis jiroveci pneumonia, treatment and prophylaxis of toxoplasmosis, traveler's diarrhea

Pregnancy Category C
Contraindicated in late pregnancy (see Key Points)

Dosing
- Adults:
  - Most indications: 1 DS tablet or equivalent (800 mg sulfamethoxazole/160 mg trimethoprim) twice daily
  - Urinary tract infections: 1 DS tablet twice daily
  - *Pneumocystis* prophylaxis: 1 DS tablet daily or three times a week; 1 SS (400 mg sulfamethoxazole/80 mg trimethoprim) daily
  - Toxoplasmosis prophylaxis: 1 DS tablet daily
  - Toxoplasmosis treatment: 5 mg/kg twice daily
  - *P. jiroveci* pneumonia: 15–20 mg/kg per/day of trimethoprim component divided into three to four doses

- Pediatrics:
  - Most indications: 8–10 mg/kg per day of trimethoprim component divided into three to four doses
  - *P. jiroveci* pneumonia: Same as adult dosing
- Renal dosage adjustment:
  - CrCl of 15–30 ml/min: 50% of the usual dose
  - Listed as contraindicated with CrCl < 15 ml/min but is sometimes still given in lower doses

Adverse Reactions: Most Common

Nausea, vomiting, anorexia, rash, urticaria, hyperkalemia, arthralgia, myalgia, hepatitis

Adverse Reactions: Rare/Severe/Important

Toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, bone marrow suppression, crystalluria, renal failure, anaphylaxis

Major Drug Interactions

Trimethoprim/Sulfamethoxazole's Effect on Other Drugs

- Thiazides: Concomitant use has been associated with thrombocytopenia with purpura in elderly patients
- Phenytoin: Increased half-life by 39%
- Methotrexate: Increased free concentrations
- Oral hypoglycemic agents: Potentiated hypoglycemia
- Digoxin: Serum levels may increase

Counseling Points

- Take oral product with a full glass of water
- Monitor for signs of hypersensitivity

Key Points

- Dosing is based on the trimethoprim component
- The combination is commonly abbreviated as *TMP–SMX*, *TMP–SMZ*, or *cotrimoxazole*
- The 5:1 ratio of sulfamethoxazole to trimethoprim is consistent among all dosage forms
- Trimethoprim competes with creatinine for renal secretion. Serum creatinine values may increase during therapy but not reflect true renal dysfunction. However, trimethoprim/sulfamethoxazole can lead to renal dysfunction through crystallization or acute interstitial nephritis.
- Trimethoprim/sulfamethoxazole is pregnancy category C, but it is contraindicated during late-stage pregnancy because sulfonamides can lead to kernicterus in the newborn. For some patients, the benefits of therapy may outweigh this risk because infection in the mother can have dire consequences for the fetus.

GLYCOPEPTIDES

Introduction

The glycopeptides are cell-wall synthesis inhibitors of Gram-positive organisms. The rise of antimicrobial resistance among *S. aureus* led to vancomycin becoming one of the most commonly used antibiotics in hospitals. The poor bioavailability of vancomycin necessitates IV therapy for systemic infections, although it is given orally for *Clostridium difficile* infections of the colon. The long half-life of the newer glycopeptides, dalbavancin and oritavancin, allow them to be given as a single IV infusion for the treatment of bacterial skin and skin-structure infection.

Mechanism of Action for the Drug Class

Glycopeptides bind to D-alanyl-D-alanine in the growing bacterial cell wall, preventing the elongation of peptidoglycan strands and halting cell wall synthesis. They are only effective against Gram-positive organisms.

Members of the Drug Class

In this section: Vancomycin
Others: Dalbavancin, oritavancin, teicoplanin (outside of the United States), telavancin (a lipoglycopeptide)

Vancomycin

Brand Name

Vancocin

Generic Name

Vancomycin

Rx Only

Dosage Forms

Injection, capsule

Usage

- Injection: *Treatment of systemic infections caused by Gram-positive organisms, including those of the respiratory tract, bloodstream, skin and skin-structure, gastrointestinal system, and genitourinary tract*
- Oral: *C. difficile infection*

Pregnancy Category B (Oral) and C (Injection)

Dosing

- Oral: 125–500 mg every 6 hours
- Injection:
  - Adults: 15–20 mg/kg twice daily
  - Pediatrics: 10 mg/kg per dose given every 6 hours
  - Infants: Loading dose of 15 mg/kg followed by 10 mg/kg every 12 hours (first week of life) or every 8 hours (> 1 week of life up to 1 month of life)
  - Doses are individualized by patient characteristics, infection severity, and renal function
- Renal dosage adjustment: Dose of the intravenous formulation needs to be reduced based on creatinine clearance. Most clinicians reduce doses of vancomycin at a CrCl of 50–60 ml/min.

Pharmacokinetic Monitoring

- Therapeutic troughs are generally considered to be from 10–20 mg/l, depending on characteristics of the infecting organism and the type of infection. Troughs of > 15–20 mg/l are associated with nephrotoxicity.
- Peaks are no longer routinely monitored
- Evidence correlating vancomycin concentrations with efficacy is imperfect

Adverse Reactions: Most Common

Infusion related: "red man syndrome" (rash, flushing, tachycardia, hypotension), phlebitis, nephrotoxicity (higher doses)

Adverse Reactions: Rare/Severe/Important

Bone marrow suppression (rare), hypersensitivity (rare)

Major Drug Interactions

Drugs Affecting Vancomycin

Nephrotoxic or ototoxic agents: Enhanced toxicity

Vancomycin's Effect on Other Drugs

Anesthesia: May result in enhanced histamine release and rash

Counseling Point

Nurses: Administer vancomycin at a rate of 1 g/hour to prevent infusion-related toxicity

Key Points

- Vancomycin is a drug of choice for infections caused by MRSA
- If red man syndrome occurs, it may be ameliorated by slowing the rate of infusion
- Closely monitor vancomycin patients on concomitant nephrotoxic or ototoxic agents
- Vancomycin oral therapy is ineffective for the treatment of systemic infection and should only be used to treat *Clostridium difficile* infection
- Vancomycin systemic therapy is ineffective for the treatment of enterocolitis or pseudomembranous colitis

LINCOSAMIDES

Introduction

Clindamycin is the only commonly used lincosamide. Clindamycin has good activity against staphylococci, streptococci, and anaerobic organisms. It is being used more frequently for the treatment of skin infections due to the increase in MRSA infections seen in the community.

Mechanism of Action for the Drug Class

Clindamycin binds to the 50S subunit of bacterial ribosomes, suppressing protein synthesis.

Members of the Drug Class

In this section: Clindamycin
Other: Lincomycin

◉ Clindamycin

Brand Name

Cleocin

Generic Name

Clindamycin

Rx Only

Dosage Forms

Capsule, injection

Usage

Skin and skin-structure infections, aspiration pneumonia, intra-abdominal infections

Pregnancy Category B

Dosing

- Adults:
  - Oral: 150–450 mg every 6 to 8 hours
  - IV: 300–900 mg every 6 to 8 hours

- Pediatrics: 8–20 mg/kg per day oral or IV into 3 to 4 divided doses
- Hepatic dosage adjustment: In patients with moderate to severe hepatic dysfunction, consider reducing the dose or extending the dosing interval

Adverse Reactions: Most Common

Abdominal pain, diarrhea, nausea, vomiting, rash, pruritus

Adverse Reactions: Rare/Severe/Important

Pseudomembranous colitis, hypersensitivity, jaundice, severe skin eruption

Major Drug Interactions

Clindamycin's Effect on Other Drugs

Neuromuscular blocking agents: Enhanced neuromuscular blockade

Counseling Point

To avoid esophageal irritation, take clindamycin capsules with a full glass of water

Key Points

- **Black Box Warning:**
  - *C. difficile*–associated disease, including pseudomembranous colitis, has been associated with all classes of antibiotics, but clindamycin is perhaps most closely associated with it in the minds of many clinicians. It is a popular exam question.
- Clindamycin is no longer recommended first-line for the treatment of intra-abdominal infections due to increasing resistance among *Bacteroides fragilis*, a common anaerobic pathogen associated with this infection type
- Many, but not all, strains of MRSA are susceptible to clindamycin. Community-associated strains are much more likely to be susceptible than hospital-acquired strains. Unlike trimethoprim-sulfamethoxazole, clindamycin is active against both strains of MRSA and most streptococci that cause skin infections.
- In addition to the *C. difficile*–associated disease risk that it causes, like many antibiotics, clindamycin commonly causes diarrhea that is not related to *C. difficile*

MACROLIDES

Introduction

Macrolides are antibiotics commonly used for respiratory tract infections. Although they are generally well tolerated, clarithromycin and erythromycin are strong inhibitors of the cytochrome P450 enzyme system, and clinicians must be wary of drug interactions with them.

Mechanism of Action for the Drug Class

Macrolides inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit

Adverse Reactions for the Drug Class: Most Common

Nausea, diarrhea, abdominal pain, pain at injection site (IV), rash, elevated liver function tests

Adverse Reactions for the Drug Class: Rare/Severe/Important

Allergic reaction, QTc prolongation

Members of the Drug Class

In this section: Azithromycin, clarithromycin, erythromycin
Others: Dirithromycin, troleandomycin

◉ Azithromycin

Brand Names

Zithromax, Z-pak, Zmax

Generic Name

Azithromycin

Rx Only

Dosage Forms

Capsule, tablet, suspension, injection

Usage

Community-acquired upper and lower respiratory tract infections, chlamydia, treatment and prophylaxis of *Mycobacteria avium intracellulare complex (MAI or MAC),* skin and skin-structure infections, syphilis

Pregnancy Category B

Dosing

- Adults:
  - Most indications: 500 or 250 mg once daily
  - Z-pak is 500 mg on day 1, followed by 250 mg on days 2 to 5
  - Zmax is a single 2 g dose
  - Prevention of MAC: 1200 mg once weekly
  - Treatment of disseminated MAC: 600 mg daily
- Pediatrics:
  - Most indications: 5–12 mg/kg once daily
  - Otitis media can be 30 mg/kg once

Adverse Reactions: Most Common

Pain at injection site (IV)

Major Drug Interactions

In drug interaction studies, azithromycin has not been reported to result in metabolic interactions associated with other macrolides. However, monitoring is suggested in patients receiving digoxin, theophylline, ergotamine derivatives, triazolam, warfarin, and other agents known to be metabolized via the cytochrome P450 enzyme system.

Counseling Points

- Immediate-release suspension and tablet can be taken without regard to food, while the extended-release suspension should be administered on an empty stomach (at least one hour before or 2 hours after a meal)
- Parenteral product should not be given as a bolus injection or intramuscularly
- Patients who vomit immediately after taking azithromycin may need to be redosed, but they should not do this without consulting their healthcare provider

Key Points

- Rising resistance rates to macrolides in *Streptococcus pneumoniae* have led to decreased efficacy for azithromycin. It should not be used as monotherapy in severely ill patients with pneumonia.
- Azithromycin has a very long terminal half-life, which allows for short-course therapy for many indications
- Increasing resistance to macrolides in *Treponema pallidum* have led to azithromycin treatment failures. It should not be used for the treatment of early Syphilis or used with caution if alternative therapies are not feasible.
- In 2012, the FDA published a warning that azithromycin therapy was associated with a small but increased risk of cardiovascular death compared with some other antibiotics. This prompted a warning to clinicians about the concern, but no specific recommendation was offered except to be aware of possible QTc prolongation and arrhythmias with antibiotic use.

◉ Clarithromycin

Brand Names

Biaxin, Biaxin-XL

Generic Name

Clarithromycin

Rx Only

Dosage Forms

Tablet, extended-release tablet, suspension

Usage

Community-acquired upper and lower respiratory tract infections, skin and skin-structure infections, treatment of MAI or MAC, treatment of *H. pylori infection* (in combination with amoxicillin and omeprazole or lansoprazole)

Pregnancy Category C

Dosing

- Adults:
  - Most indications: 250–500 mg every 12 hours
  - Extended-release: 1000 mg every 24 hours
- Pediatrics: 7.5 mg/kg every 12 hours
- Renal dosage adjustment: Dose adjusted with a CrCl < 30 ml/min

Adverse Reactions: Most Common

Altered taste

Adverse Reactions: Rare/Severe/Important

Prolonged QTc interval (especially when administered with concomitant drugs that prolong the QTc interval); severe hepatic dysfunction

Major Drug Interactions

Drugs Affecting Clarithromycin

Ritonavir will increase the concentration of clarithromycin by 77% and its metabolite by 100%

Clarithromycin's Effect on Other Drugs

- Theophylline concentrations: Increase by 20% on average
- Carbamazepine levels will increase
- Warfarin: Enhanced anticoagulant effect
- Digoxin levels: Increase significantly
- Ergot derivatives: May result in acute ergot toxicity; combination is contraindicated
- QTc-prolonging drugs: Potentiated QTc prolongation, possibly leading to polymorphic ventricular tachycardia

Contraindications

Concomitant administration with cisapride, pimozide, terfenadine, and ergotamine or dihydroergotamine

Counseling Points

- Take tablets and suspension without regard to meals
- Take extended-release tablets with food

Key Points

- Drug interactions reported with erythromycin are likely to occur with clarithromycin
- Patients receiving drugs that are metabolized by the cytochrome P450 enzyme system should be closely monitored

Erythromycin

Brand Names
Ery-Tab, E-Mycin, EES, EryPed, Ilosone

Generic Name
Erythromycin

Rx Only

Dosage Forms
Ophthalmic ointment; topical ointment, gel, and solution; multiple oral formulations; injection

Usage
Community-acquired upper and lower respiratory tract infections, skin and skin-structure infections, chlamydia, conjunctivitis, preoperative bowl preparation

Pregnancy Category B

Dosing
- Adults:
  - Mild to moderate infection: 250–500 mg 4 times daily
  - Severe infection: 500–1000 mg every 6 hours
- Pediatrics:
  - Mild to moderate infection: 7.5–12.5 mg (base)/kg four times daily
  - Severe infection: 15–25 mg/kg (base) 4 times daily

Adverse Reactions: Most Common
Infusion-site pain (IV), phlebitis, prolonged QTc interval, diarrhea

Adverse Reactions: Rare/Severe/Important
Hepatotoxicity (estolate form), ototoxicity (high dose)

Major Drug Interactions
Erythromycin's Effect on Other Drugs
- Carbamazepine, valproic acid: Increased levels
- Cyclosporine: Increased levels
- Ergot derivatives: Increased levels (contraindicated)
- Many HMG-CoA reductase inhibitors: Increased risk of rhabdomyolysis
- Midazolam, triazolam: Decreased clearance, prolonged sedative effect
- Theophylline: Increased concentrations
- Warfarin: Potentiated anticoagulant effect
- QTc-prolonging drugs: Potentiated QTc prolongation, possibly leading to polymorphic ventricular tachycardia

Counseling Points
- Take with a full glass of water
- Report persistent abdominal pain (> 3 days duration)
- Report any changes in hearing function

Key Points
- Dosing varies based on the specific salt used
- Erythromycin is commonly used off-label as a promotility agent because it directly stimulates motilin receptors in the gut. This effect also causes more diarrhea with erythromycin than with other macrolides.
- Patients receiving drugs that are metabolized by the cytochrome P450 enzyme system should be monitored closely

NITROFURANS

Introduction
Nitrofurantoin is the only available nitrofuran. It has one use, the treatment of acute uncomplicated cystitis (a urinary tract infection). Therapeutic concentrations of nitrofurantoin are not reached anywhere in the body but the bladder. It has become more useful over time as resistance to fluoroquinolones, trimethoprim/sulfamethoxazole, and other first-line drugs has increased, particularly in *E. coli*.

Mechanism of Action for the Drug Class
The mechanism of nitrofurantoin is not exactly known, but it is known to inhibit several bacterial enzyme systems, including acetyl coenzyme A, thus interfering with metabolism and possibly cell-wall synthesis

Nitrofurantoin

Brand Names
Macrodantin, Macrobid

Generic Names
Nitrofurantoin, nitrofurantoin macrocrystals (Macrobid)

Rx Only

Dosage Form
Capsule

Usage
Urinary tract infections (acute uncomplicated cystitis)

Pregnancy Category B

Contraindicated at term (see Key Points)

Dosing

- Macrobid: 100 mg twice daily
- Macrodantin: 50–100 mg 4 times daily
- Renal dosage adjustment: Contraindicated in patients with a CrCl < 60 ml/min

Adverse Reactions: Most Common

Nausea, headache, diarrhea, rash, dizziness

Adverse Reactions: Rare/Severe/Important

Chronic, subacute, or acute pulmonary hypersensitivity; hepatic toxicity; lupus-like syndrome; exfoliative dermatitis; peripheral neuropathy (may be irreversible); cholestatic jaundice

Major Drug Interactions

Drugs Affecting Nitrofurantoin

- Antacids containing magnesium trisilicate: Decreased absorption of nitrofurantoin
- Probenecid: Increased nitrofurantoin levels

Counseling Point

Take with food to enhance tolerability and absorption

Key Points

- Nitrofurantoin therapy will produce a false-positive urine glucose test
- Not for use for any infection other than uncomplicated cystitis
- Unlike fluoroquinolones and trimethoprim/sulfamethoxazole, nitrofurantoin is pregnancy category B and often is used in pregnant women. However, it can cause hemolytic anemia in newborns and should be avoided in pregnant women who are at term.

NITROIMIDAZOLES

Introduction

Metronidazole is the only commonly used nitroimidazole. It is unique in that it only has clinically useful activity against anaerobic organisms and is thus frequently used in anaerobic infections. It is also a drug of choice for treating *C. difficile* infections.

Mechanism of Action for the Drug Class

In susceptible organisms, metronidazole is reduced to unidentified polar products, which result in cytotoxic antimicrobial effects.

Members of the Drug Class

In this section: Metronidazole
Other: Tinidazole

◉ Metronidazole

Brand Name

Flagyl

Generic Name

Metronidazole

Rx Only

Dosage Forms

Tablet, extended-release tablet, capsule, injection, topical gel

Usage

Treatment of anaerobic bacterial infections, C. difficile infection, trichomoniasis, amebiasis, giardiasis, bacterial vaginosis, pelvic inflammatory disease, rosacea, *Helicobacter pylori* infection (in combination with other drugs), prophylaxis in gastrointestinal surgery

Pregnancy Category B

Dosing

- Adults:
  - Most indications: 250–500 mg oral or IV two to four times daily
  - Trichomoniasis: Can be treated with 2000 mg orally once
- Pediatrics: 15–50 mg/kg per day into 3 divided doses

- Hepatic dosage adjustment: In patients with moderate to severe hepatic dysfunction, consider reducing the dose or extending the dosing interval

Adverse Reactions: Most Common

Nausea, metallic taste, peripheral neuropathy

Adverse Reactions: Rare/Severe/Important

Pancreatitis, hypersensitivity, stomatitis, confusion, dizziness, seizures

Major Drug Interactions

Drugs Affecting Metronidazole

- Alcohol: May result in a mild disulfiram reaction
- Phenobarbital: Decreased half-life of metronidazole

Metronidazole's Effect on Other Drugs

- Warfarin: Potentiated anticoagulant effect, possibly leading to bleeding events
- Disulfiram: Acute psychosis and confusion
- Lithium: Increased levels

Counseling Points

- Be aware of possible metallic taste
- Minimize alcohol intake due to potential mild disulfiram reaction

Key Points

- Studies have shown that metronidazole is inferior to oral vancomycin for the treatment of *C. difficile* infection. It is generally used as a first-line agent in mild to moderate cases due to its significantly lower cost. Unlike vancomycin, it can be given intravenously for *C. difficile* infection and is an option in patients with a bowel obstruction.
- Metronidazole has excellent bioavailability and is given in similar oral and intravenous doses
- Metronidazole also is given intravaginally to treat bacterial vaginosis

OXAZOLIDINONES

Introduction

The Oxazolidinones have broad Gram-positive activity including activity against MRSA and vancomycin-resistant enterococci (VRE). Linezolid and tedizolid are the two drugs in this class and both have excellent bioavailability and are available IV and PO. Linezolid is commonly used for MRSA pneumonia.

Mechanism of Action for the Drug Class

Oxazolidinones bind to the 50S ribosomal subunit, preventing translation and inhibiting protein synthesis. They have activity against many Gram-positive organisms, some atypical, and *Mycobacterium tuberculosis*.

Members of the Drug Class

In this section: Linezolid
Others: Tedizolid

◉ Linezolid

Brand Name(s)

Zyvox

Generic Name

Linezolid

Rx Only

Dosage forms

Tablet, oral suspension, injection

Usage

Lower respiratory tract infections, skin and skin structure infections, endocarditis, CNS infections, bone and joint infections, tuberculosis (as part of a multidrug regimen)

Pregnancy Category C

Dosing

- Adults: 600 mg every 12 hours
- Pediatrics: 10 mg/kg every 8 hours (maximum of 600 mg/dose)

Adverse Reactions

Diarrhea, nausea, vomiting, headache

Adverse Reactions: Rare/Severe/Important

Bone marrow suppression (most commonly thrombocytopenia), peripheral and optic neuropathy, serotonin syndrome

Major Drug Interactions

Linezolid's Effect on Other Drugs

Serotonergic agents: increased serotonergic effects

Contraindications

Concurrent use or within 2 weeks of MAO-inhibitors

Essential Monitoring Parameters

Complete blood counts, particularly after 10–14 days of therapy

Counseling Point

Avoid concurrent serotonergic drug use, if possible; if the interaction cannot be avoided, monitor for signs and symptoms of serotonin syndrome

Key Points

- Linezolid is not preferred in the treatment of infections requiring > 2 weeks of treatment due to hematologic and neurologic toxicity
- Oxazolidinones are inhibitors of monoamine oxidase and can cause serotonin syndrome when given with serotonergic modulators
- Linezolid has excellent absorption and is given in equivalent doses orally and intravenously

PENICILLINS

Introduction

Penicillins were the second class of antibiotics to be developed. They comprise a very large class of antibiotics and range from agents with broad antimicrobial spectra to those with a more narrow spectrum. Some agents in this class can be given orally.

Mechanism of Action for the Drug Class

Penicillins limit bacterial cell growth in susceptible bacteria by inhibiting transpeptidase enzymes (also known as penicillin-binding proteins). This prevents cross-linking of peptidoglycan strands, thereby inhibiting synthesis of the bacterial cell wall.

Adverse Reactions for the Drug Class: Most Common

Nausea, vomiting, diarrhea, rash

Adverse Reactions for the Drug Class: Rare/Severe/Important

Hypersensitivity, anaphylaxis, seizures, pseudomembranous colitis

Major Drug Interactions for the Drug Class

Drugs Affecting Penicillins

- Probenecid: Decreases the renal tubular secretion of penicillins, resulting in increased and prolonged serum concentrations
- Chloramphenicol, macrolides, sulfonamides, and tetracyclines interfere with the bactericidal effects of penicillins

Counseling Point for the Drug Class

Report any signs of an allergic reaction, such as a rash or hives, to your healthcare provider immediately

Key Point for the Drug Class

Use with caution in patients who are allergic to other beta-lactam antibiotics

Members of the Drug Class

In this section: Amoxicillin, amoxicillin/clavulanate, penicillin, piperacillin/tazobactam

Others: Ampicillin, cloxacillin, dicloxacillin, nafcillin, oxacillin

◉ Amoxicillin

Brand Names

Amoxil, Trimox

Generic Name

Amoxicillin

Rx Only

Dosage Forms

Capsule, tablet, suspension

Usage

Upper respiratory tract infections, urinary tract infections, skin and skin-structure infections, *Helicobacter pylori infection*

Dosing

- Adults:
  - Mild to moderate infections: 250 mg thrice daily or 500 mg twice daily
  - Moderate to severe infections: 500 mg thrice daily or 875 mg twice daily

- Pediatrics:
  - Otitis media: 80–90 mg/kg per day in 2 divided doses
  - Less-severe infections: 25–50 mg/kg/day in 3 divided doses (maximum of 500 mg/dose)
- Renal dosage adjustment: Adjust with a CrCl of < 30 ml/min

Pregnancy Category B

Key Points

- Amoxicillin and ampicillin have nearly identical antimicrobial spectra, but amoxicillin has much better oral absorption
- Resistance to amoxicillin among *Escherichia coli* is high, so it is not an ideal choice for urinary tract infections. If susceptibility information is not known, amoxicillin/clavulanate is a better choice for most patients.

◉ Amoxicillin/Clavulanate

Brand Name

Augmentin

Generic Name

Amoxicillin/clavulanate

Rx Only

Dosage Forms

Tablet, suspension

Usage

Upper and lower respiratory tract infections, skin and skin structure infections, urinary tract infections, mixed aerobic and anaerobic infections

Pregnancy Category B

Dosing

- Dosing is based on the amoxicillin component
- Adults:
  - Mild to moderate infections: 250 mg thrice daily or 500 mg twice daily
  - Moderate to severe infections: 500 mg thrice daily or 875 mg twice daily
- Pediatrics:
  - Otitis media: 90 mg/kg per day in 2 divided doses
  - Less severe infections: 25 mg/kg/day in 2 divided doses or 20 mg/kg/day in 3 divided doses
- Renal dosage adjustment: Adjust with a CrCl < 30 ml/min

Counseling Point

To minimize adverse gastrointestinal events, take at the start of a meal

Key Points

- Twice-daily dosing is associated with significantly less diarrhea
- The 250 mg and 500 mg tablets contain the same quantity of clavulanic acid; therefore, do not substitute two 250 mg tablets for one 500 mg tablet
- Amoxicillin/clavulanate has a significantly broader antimicrobial spectrum than amoxicillin alone. That is advantageous in treating some potentially drug-resistant infections but is not needed in those likely to be drug susceptible.

◉ Penicillin

Brand Names

Beepen-VK, Pen-VK, Veetids

Generic Name

Penicillin

Rx Only

Dosage Forms

Tablet, oral solution, injection (IM and IV)

Usage

Streptococcal infections, uncomplicated anthrax, necrotizing ulcerative gingivitis, prophylaxis of pneumococcal infections, prophylaxis of recurrent rheumatic fever, syphilis

Pregnancy Category B

Dosing

- 250–500 mg two to thrice daily
- Renal dosage adjustment: If CrCl < 10 or dialysis, administer twice daily

◉ Piperacillin/Tazobactam

Brand Name

Zosyn

Generic Name

Piperacillin/Tazobactam

Rx Only

Dosage Forms

Injection

Usage

Upper and lower respiratory tract infections, intra-abdominal infections, skin and skin-structure infections, urinary tract infections, pelvic inflammatory disease, bacteremia, endocarditis, bone and joint infections, surgical prophylaxis

Pregnancy Category B

Dosing

- Adults:
  - Conventional dosing: 3.375 g every 6 hours or 4.5 g every 6 to 8 hours
  - Extended infusion dosing: 3.375 to 4.5 g over 4 hours every 8 hours
- Pediatrics: Based on the piperacillin component
  - 80–100 mg/kg/dose every 8 hours
- Renal dosage adjustment: Adjust with a CrCl < 40 ml/min for conventional dosing and CrCl < 20 ml/min for extended infusion dosing

Key Points

- Piperacillin/tazobactam has activity against *Pseudomonas aeruginosa* and is advantageous in treating hospital-acquired infections and some drug-resistant infections
- Due to its broad spectrum, piperacillin/tazobactam is frequently used for empiric treatment in hospital-acquired infections

TETRACYCLINES

Introduction

Tetracyclines are broad-spectrum antibiotics that have lost much of their utility due to increases in bacterial resistance. They are still useful for many indications; however, and they are drugs of choice in several tick-borne diseases.

Mechanism of Action for the Drug Class

Tetracyclines inhibit bacterial protein synthesis by reversibly binding to the 30S ribosomal subunit, resulting in a bacteriostatic effect.

Pregnancy Category D for the Drug Class

Adverse Reactions for the Drug Class: Most Common

Nausea, vomiting, diarrhea, gastrointestinal pain, rash, photosensitivity reactions, dizziness

Adverse Reactions for the Drug Class: Rare/Severe/Important

Hypersensitivity, tooth discoloration with prolonged use

Major Drug Interactions for the Drug Class

Drugs Affecting Tetracyclines

- Di- and trivalent cations: Greatly decrease absorption of tetracyclines

Tetracyclines' Effects on Other Drugs

- Concurrent use of tetracyclines and methoxyflurane has been reported to result in fatal renal toxicity
- Enhance the activity of warfarin
- Diminish effect of cell-wall active bactericidal antibiotics when used concomitantly (e.g., beta-lactams)
- May render oral contraceptives less effective

Counseling Points for the Drug Class

- Administration to children is likely to result in discoloration of the teeth, particularly with prolonged use. Use in children 8 years of age and younger only when the benefit outweighs the risk.
- Dispose of all unused medication; use of outdated tetracycline products may result in Fanconi syndrome, a disorder characterized by kidney damage
- Separate from multivalent cation–containing compounds (including milk) by at least 2 hours

Members of the Drug Class

In this section: Doxycycline, minocycline
Others: Demeclocycline, tetracycline, tigecycline (a glycylcycline)

◉ Doxycycline

Brand Name

Vibramycin

Generic Name

Doxycycline

Rx Only

Dosage Forms

Capsule, suspension, injection

Usage

Community-acquired upper and lower respiratory tract infections, chlamydia, Rocky Mountain spotted fever, typhus fever, Q fever, rickettsialpox, tick fevers caused by rickettsiae, Lyme disease, plague, tularemia

Dosing

- Adults: 100 mg twice daily
- Pediatrics (≥ 8 years of age): 2–4 mg/kg/day divided every 12–24 hours oral or IV

Minocycline

Brand Names

Dynacin, Minocin, Solodyn (extended-release formulation)

Generic Name

Minocycline

Rx Only

Dosage Forms

Capsule, tablet, suspension, injection

Usage

Community-acquired upper and lower respiratory tract infections, *acne, skin and soft tissue infections,* Rocky Mountain spotted fever, typhus fever, Q fever, rickettsialpox, Lyme disease, plague, tularemia

Dosing

- Normal-release formulation
  - Adults: 200 mg once, then 100 mg twice daily
  - Pediatrics (> 8 years of age): 4 mg/kg once, then 2 mg/kg twice daily oral or IV
- Extended-release formulation: 45–135 mg once daily, based on weight
- Renal dosage adjustment: Use not recommended in renal failure

Key Point

Extended-release minocycline is only approved for the treatment of acne. The normal-release formulation of minocycline is used for this indication as well.

ANTIMYCOBACTERIAL AGENTS

Introduction

Mycobacteria, such as *Mycobacterium tuberculosis,* have cell walls that have a very different anatomy than other bacteria. Many antibiotics are not active against mycobacteria. Isoniazid and rifampin are both highly active against *M. tuberculosis* and are the two most important drugs in the treatment of tuberculosis. They are often used in combination in the treatment of tuberculosis, usually with other agents as well.

Mechanism of Action for the Drug Class

Isoniazid inhibits the synthesis of mycolic acids, an essential component of the mycobacterial cell wall. Rifampin inhibits the synthesis of RNA by preventing the action of RNA polymerase. Its activity is not specific to mycobacteria.

Members of the Drug Class

In this section: isoniazid, rifampin
Others: ethambutol, pyrazinamide, rifabutin, rifapentine

Isoniazid

Brand Names

Laniazid, Nydrazid

Generic Name

Isoniazid

Rx Only

Dosage Forms

Tablet, oral solution, injection

Usage

Treatment of active and latent tuberculosis

Pregnancy Category C

Dosing

- Active tuberculosis: 5 mg/kg daily (maximum of 300 mg/dose) or 15 mg/kg 2 to 3 times weekly (maximum of 900 mg/dose)
- Latent tuberculosis: 5 mg/kg daily (maximum of 300 mg/dose)
- Hepatic impairment: In patients with moderate to severe hepatic dysfunction, consider reducing the dose or extending the dosing interval

Adverse Reactions: Most Common

Peripheral neuropathy, elevated liver function tests, abdominal pain

Adverse Reactions: Rare/Severe/Important

Hepatitis, hypersensitivity, anemia, thrombocytopenia, systemic lupus erythematosus

Major Drug Interactions

Drugs Affecting Isoniazid

- Cycloserine, ethionamide: Potentiated nervous system toxicity
- Ethanol: Increased hepatotoxicity

Isoniazid's Effect on Other Drugs

- Carbamazepine: Increased levels
- Phenytoin: Increased levels

- Serotonergic agents: Potential serotonin syndrome secondary to the weak MAO-inhibiting effect of isoniazid

Counseling Points

- Avoid alcohol intake while on isoniazid to prevent liver damage
- Report persistent abdominal pain (≥3 days), dark urine, fever, or fatigue because those symptoms may be signs of liver problems

Key Points

- **Black Box Warning:**
  - Severe and fatal hepatitis associated with isoniazid is possible
- For treatment of active tuberculosis, must be part of a multidrug regimen
- Administer with pyridoxine (vitamin B_6) to prevent peripheral neuropathy
- Common abbreviation is INH

◉ Rifampin

Brand Names

Rifadin, Rimactane

Generic Name

Rifampin

Rx Only

Dosage Forms

Capsule, injection

Usage

Active and latent tuberculosis, treatment of asymptomatic carriers of *N. meningitidis,* synergistic therapy for various infections (such as endocarditis) with other antibiotics

Pregnancy Category C

Dosing

- 600 mg IV or PO every 24 hours
- Hepatic impairment: In patients with moderate to severe hepatic dysfunction, consider reducing the dose or extending the dosing interval

Adverse Reactions: Most Common

Nausea, vomiting, cramps, rash, fever, drowsiness, elevated liver function tests

Adverse Reactions: Rare/Severe/Important

Hypersensitivity, hyperbilirubinemia, thrombocytopenia

Major Drug Interactions

Drugs Affecting Rifampin

- Antacids: May reduce absorption of rifampin
- Cotrimoxazole: May increase the levels of rifampin
- Isoniazid or halothane: Potentiate hepatotoxicity

Rifampin's Effect on Other Drugs

- Rifampin is a potent inducer of many hepatic enzymes, particularly those of the cytochrome P450 system. Careful monitoring of patients on concomitant drugs that are metabolized via the liver is recommended.
- Examples of drugs that are known to be cleared more rapidly by rifampin include phenytoin, disopyramide, quinidine, warfarin, apixaban, rivaroxaban, dabigatran, edoxaban, protease inhibitors, azole antifungals, diltiazem, nifedipine, barbiturates, beta blockers, chloramphenicol, clarithromycin, digoxin, oral contraceptives, doxycycline, oral hypoglycemic agents, levothyroxine, methadone, narcotic analgesics, tricyclic antidepressants, tacrolimus, cyclosporine, and theophylline. Decreased therapeutic effects of these drugs are common with coadministration.

Counseling Point

Rifampin will turn bodily fluids orange or red. This includes tears, urine, and sweat. Contact lenses may be permanently stained by this red color and should not be worn during rifampin therapy.

Key Points

- Always screen patients for drug interactions when rifampin therapy is started. If interactions cannot be avoided, careful monitoring is required.
- Rifabutin is a related drug with somewhat less potent enzyme induction that may be used in place of rifampin for some indications
- In the treatment of active tuberculosis, combination therapy is always needed. Rifampin cannot be used alone.
- Unlike most other antimycobacterial drugs, rifampin's activity is not limited to mycobacteria. It is sometimes used in combination with other antibacterial drugs for the treatment of resistant or difficult-to-treat bacterial infections.

ANTIFUNGALS, POLYENES

Introduction

Polyenes are one of the oldest classes of antifungals. Two agents are available: amphotericin B, which is given systemically; and nystatin, which is given as topical therapy only. Neither drug can be given orally for systemic fungal infections. Adverse reactions with IV amphotericin B are considerable.

Mechanism of Action for the Drug Class

Polyenes bind to ergosterol in the fungal cell wall, causing cell-wall instability and leakage of cytoplasmic contents

Members of the Drug Class

In this section: Amphotericin B, nystatin

◉ Amphotericin B

Brand Names

Amphocin, Fungizone

Generic Name

Amphotericin B deoxycholate

Rx Only

Dosage Form

Injection

Usage

Systemic fungal infections caused by yeasts, molds, and dimorphic fungi; empiric antifungal therapy in febrile neutropenia; leishmaniasis

Pregnancy Category B

Dosing

- 0.3–1.5 mg/kg per day
- Note: Lipid formulations of amphotericin B are available and are given in much higher doses (typically 3–5 mg/kg/day). Fatal overdoses have occurred when the incorrect formulation has been given at the incorrect dose.

Adverse Reactions: Most Common

Nephrotoxicity, electrolyte wasting (primarily potassium and magnesium), infusion reactions (fever, chills, nausea, flushing, tachycardia, hypotension)

Adverse Reactions: Rare/Severe/Important

Bronchospasm, hypoxia, arrhythmias, anemia, hypersensitivity

Major Drug Interactions

Drugs Affecting Amphotericin B

- Concomitant nephrotoxic agents potentiate nephrotoxicity
- Corticosteroids: May potentiate the potassium-wasting effect

Key Points

- Premedicate with diphenhydramine and/or acetaminophen to minimize infusion reactions
- Ensure adequate hydration by providing boluses of saline before and after the infusion to reduce the incidence of nephrotoxicity
- Infuse over at least 2 hours to decrease infusion-related reactions
- Lipid formulations of amphotericin B are commercially available. Those agents tend to have a better adverse-event profile. Recommended dosing and administration is quite different for those products.

◉ Nystatin

Brand Name

Mycostatin

Generic Name

Nystatin

Rx Only

Dosage Forms

Suspension, powder, oral and vaginal tablets, cream, ointment

Usage

Treatment and prophylaxis of cutaneous, mucocutaneous, and superficial candidal infections

Pregnancy Category C (Oral and Topical) and A (Vaginal)

Dosing

- Suspension: 400,000–600,000 units 4 times daily. Patient should swish in the mouth before swallowing when treating oral candidiasis.
- Topical: Apply 2 to 3 times daily to affected area
- Vaginal: One vaginal tablet daily at bedtime

Adverse Reactions: Most Common

Mild nausea, vomiting (tablet)

Counseling Points

- Do not apply in large quantity to open wound
- Cover medicated area with a gauze or bandage

Key Point

Not effective for systemic fungal infections

ANTIFUNGALS, TRIAZOLES

Introduction

The introduction of the azole antifungals changed the way systemic fungal infections were treated. The excellent bioavailability of some of those drugs allows for oral therapy of systemic infections.

Mechanism of Action of the Drug Class

Azole antifungals inhibit the production of ergosterol, a component of the fungal cell membrane, by inhibiting fungal cytochrome P450 enzymes.

Adverse Reactions for the Drug Class: Most Common

Vomiting, abdominal pain, nausea, diarrhea, rash

Adverse Reactions for the Drug Class: Rare/Severe/Important

Elevated liver function tests (rare severe hepatic toxicity), hypersensitivity

Major Drug Interactions for the Drug Class

All agents inhibit the cytochrome P450 system and increase concentrations of drugs metabolized via this pathway

Members of the Drug Class

In this section: Fluconazole, itraconazole, voriconazole
Others: Ketoconazole, numerous topical agents, posaconazole, isavuconazole

◉ Fluconazole

Brand Name

Diflucan

Generic Name

Fluconazole

Rx Only

Dosage Forms

Tablet, suspension, injection

Usage

Candida infections of the vagina, oropharyngeal cavity, esophagus, bloodstream, and visceral organs; cryptococcal meningitis

Pregnancy Category D

However, pregnancy category is C for one-time doses for vaginal infections

Dosing

- Adults:
  - 200–800 mg oral or IV once daily
    - Patients with serious infections, such as candidemia, should first receive a loading dose of twice the maintenance, then the maintenance dose 24 hours later
  - Vaginal candidiasis: 150 mg once
- Pediatrics: 3–12 mg/kg oral or IV once daily
- Renal dosage adjustment: Decrease dose 50% with CrCl < 50 ml/min

Major Drug Interactions

Drugs Affecting Fluconazole

- Hydrochlorothiazide: Increases fluconazole concentrations
- Rifampin: Decreases fluconazole concentrations

Fluconazole's Effect on Other Drugs

- Drugs metabolized via CYP450: Increased concentrations
- Warfarin: Potentiated anticoagulant effect

Counseling Point

Women being treated with fluconazole for vaginal yeast infections should be told that symptoms (such as itching and irritation) are unlikely to subside on day 1 of therapy, even though the infection is successfully treated

Key Points

- Fluconazole has high bioavailability, and oral and intravenous doses are equivalent
- Patients prescribed fluconazole should always be screened for drug interactions
- Unlike other azoles, fluconazole has appreciable renal elimination and needs to be adjusted in renal dysfunction

◉ Itraconazole

Brand Name

Sporanox

Generic Name

Itraconazole

Rx Only

Dosage Forms

Capsule, oral solution

Usage
Candidiasis, mold infections, dimorphic fungal infections, *onychomycosis*

Pregnancy Category C

Dosing
100–400 mg daily; doses > 200 mg/day should be divided into twice daily

Adverse Reactions: Most Common
Hypokalemia, rash

Adverse Reactions: Rare/Severe/Important
Negative inotropic effect, especially in patients with underlying congestive heart failure

Major Drug Interactions
Drugs Affecting Itraconazole
- Inducers of CYP450: Decrease itraconazole concentrations
- Inhibitors of CYP450: Increase itraconazole concentrations
- Antacids, H2-receptor antagonists, proton pump inhibitors: Decrease itraconazole absorption

Itraconazole's Effect on Other Drugs
- Drugs metabolized by CYP450: Increased concentrations
- Cisapride, quinidine, dofetilide: QTc prolongation via inhibition of metabolism

Contraindications
Coadministration with cisapride, pimozide, quinidine, or dofetilide; heart failure

Counseling Points
- Oral solution and capsules are not interchangeable
- Take capsules with food; can add a cola beverage to enhance bioavailability

Key Points
- **Black Box Warning:**
  - Negative inotropic effects have been observed following administration. Caution should be used in patients with risk factors for heart failure. Itraconazole should be discontinued if signs or symptoms of heart failure develop during treatment.
- Oral solution has significantly better bioavailability than oral capsules (area under the curve [AUC] increased by 149%)
- Patients prescribed itraconazole should always be screened for drug interactions
- Oral solution does not have to be taken with food; the capsules should be administered with food. In addition, acid-suppressing agents have less of an effect on the bioavailability of the oral solution.

◉ Voriconazole

Brand Name
Vfend

Generic Name
Voriconazole

Rx Only

Dosage Forms
Tablet, suspension, injection

Usage
Invasive aspergillosis, invasive candidiasis, esophageal candidiasis, *mold infections*

Pregnancy Category D

Dosing
- IV: 6 mg/kg every 12 hours twice, then 3–4 mg/kg every 12 hours
- Oral: Either same as IV dosage or 400 mg every 12 hours twice, then 200 mg every 12 hours (100 mg every 12 hours for patients < 40 kg)
- Renal dosage adjustment: Injection is not recommended for patients with a CrCl < 50 ml/min due to accumulation of the intravenous vehicle (cyclodextrin)
- Hepatic dosage adjustment:
  - Mild to moderate dysfunction (Child-Pugh class A or B): Reduce maintenance dose by 50%
  - Not recommended in severe hepatic dysfunction

Adverse Reactions: Most Common
Rash, visual events, hepatic enzyme elevations

Adverse Reactions: Rare/Severe/Important
Hepatic failure, visual hallucinations, gastrointestinal disturbances

Major Drug Interactions
Drugs Affecting Voriconazole
- Inducers of CYP450: Decrease voriconazole concentrations
- Inhibitors of CYP450: Increase voriconazole concentrations

Voriconazole's Effect on Other Drugs

Drugs metabolized by CYP450: Increased concentrations

Contraindications
Coadministration with sirolimus, rifampin, rifabutin, efavirenz, ritonavir, long-acting barbiturates, terfenadine, astemizole, cisapride, pimozide, quinidine, ergot alkaloids, carbamazepine

Counseling Points

- Visual effects are common and dose related. They usually go away after the first few doses.
- Although the IV form is relatively contraindicated with a CrCl < 50 ml/min, it may be used when the benefits of therapy outweigh the risks of cyclodextrin accumulation

Key Points

- Injection contains the solubilizer beta-cyclodextrin, which can accumulate in renal dysfunction
- Patients prescribed voriconazole should always be screened for drug interactions
- Patients on voriconazole should have their liver function tests monitored closely

ANTIVIRALS, ANTIHERPES AGENTS

Introduction

Acyclovir is a commonly used antiviral agent for many types of herpes virus infections. Due to the low bioavailability of the oral form and the need for frequent administration, the prodrug valacyclovir was developed. The only other differences between the two drugs are pharmacokinetic.

Mechanism of Action of the Drug Class

Acyclovir is a competitive inhibitor of viral DNA synthesis. Valacyclovir is a prodrug that is rapidly converted to acyclovir in vivo.

Adverse Reactions for the Drug Class: Most Common

Nausea, vomiting, diarrhea

Adverse Reactions for the Drug Class: Rare/Severe/Important

Thrombotic thrombocytopenic purpura (immunocompromised host), anaphylaxis, rash, renal failure, dizziness, agitation, crystalluria

Major Drug Interactions for the Drug Class

Drugs Affecting Acyclovir/Valacyclovir

Probenecid: Increase in the mean half-life and AUC of acyclovir

Counseling Points for the Drug Class

- Initiate therapy as soon as possible; for genital herpes, ideally during the prodromal period; other diseases, at the onset of rash
- Take oral products with a full glass of water to decrease potential for crystallization in the kidney

Members of the Drug Class

In this section: Acyclovir, valacyclovir
Other: Famciclovir

◉ Acyclovir

Brand Name

Zovirax

Generic Name

Acyclovir

Rx Only

Dosage Forms

- Oral: Capsule (200 mg); suspension (200 mg/5 ml); tablet (400 mg, 800 mg)
- Parenteral: Concentrate (25 mg/ml; 50 mg/ml); infusion (500 mg, 1 g)

Usage

Mucosal, cutaneous, ocular, and systemic herpes simplex infection, including genital herpes; varicella-zoster virus infection, including chicken pox and herpes zoster (shingles); herpes encephalitis (IV)

Pregnancy Category B

Dosing

- Genital herpes:
  - Initial episode: 200 mg 5 times daily *or* 400 mg 3 times daily for 7 to 10 days
  - Initial episode (prostatitis): 400 mg 5 times daily for 10 days *or* 800 mg 3 times daily for 7 to 10 days
  - Severe initial episode: 5–10 mg/kg IV every 8 hours for 2 to 7 days or until clinical improvement is observed, followed by oral antiviral therapy to complete a total course of at least 10 days of therapy
  - Recurrent episodes: 200 mg 5 times daily *or* 400 mg 3 daily *or* 800 mg twice daily for 5 days
  - Chronic suppressive therapy: 400 mg twice daily *or* 200 mg 3 to 5 times daily for up to 1 year
- Varicella (chicken pox): Initiate therapy within 24 to 48 hours of the appearance of rash
  - Immunocompetent children 2 years of age and older < 40 kg: 20 mg/kg 4 times daily for 5 days
  - Immunocompetent patient >40 kg: 800 mg per dose 4 times daily for 5 days
  - Herpes zoster (shingles): Initiate therapy within 24 to 48 hours of the appearance of rash

- Immunocompetent adults and children ≥ 12 years of age: 800 mg 5 times daily for 7 to 10 days
- HIV-infected patient with dermatomal zoster: 800 mg five times daily for 7 to 10 days
- Immunocompromised patients ≥ 12 years of age: 10 mg/kg IV every 8 hours for 7 days
- Immunocompromised patients ≤ 12 years of age: 20 mg/kg IV every 8 hours for 7 days

- Herpes simplex virus infection:
  - Mucosal or cutaneous infection:
    - Adults: 400 mg 5 times daily for 7 to 14 days
    - Pediatrics: 10 mg/kg/dose three times daily for 7 to 14 days
  - Parenteral:
    - Adults: 5 mg/kg IV every 8 hours for 7 days
    - Pediatrics: 10 mg/kg IV every 8 hours for 7 days
  - Encephalitis:
    - Adults ≥ 12 years of age: 10 mg/kg IV every 8 hours for at least 10 days
    - Pediatrics ≥ 12 years of age: 20 mg/kg IV every 8 hours for at least 10 days
- Renal dosage adjustment:
  - Oral therapy: Dose adjust with CrCl < 10–25 ml/min
  - IV therapy: Dose adjust with CrCl < 50 ml/min

Valacyclovir

Brand Name
Valtrex

Generic Name
Valacyclovir

Dosage Forms
Tablet

Usage
Herpes zoster infection, genital herpes (initial, recurrent, or suppressive therapy)

Dosing
- Treatment: 500–1000 mg every 8 to 12 hours
- Suppression: 500–1000 mg daily
- Renal dose adjustment: Decrease dose with a CrCl < 30–49 ml/min

ANTIVIRALS, ANTI-INFLUENZA AGENTS

Introduction
Influenza is a common, easily spread infection that is seasonal. Because it evolves so frequently, designing effective vaccines and drugs that always work is nearly impossible. Oseltamivir is an oral drug for the treatment of influenza that can shorten the duration of illness, particularly when it is started quickly after influenza symptoms begin. Like all anti-influenza agents, its effectiveness is dependent on the susceptibility of the dominant influenza strains of the season.

Mechanism of Action of the Drug Class
Oseltamivir is a neuraminidase inhibitor. It prevents the influenza viral neuraminidase enzyme from releasing new virions (viruses) from infected host cells, preventing further replication.

Members of the Drug Class
In this section: Oseltamivir
Others: Zanamivir, amantadine, rimantadine

Oseltamivir

Generic Name
Oseltamivir

Brand Name
Tamiflu

Rx Only

Dosage Form
Capsule, suspension

Usage
Treatment of influenza, prophylaxis of influenza in unvaccinated persons

Pregnancy Category C

Dosing
- Adults and children > 12 years
  - Treatment of influenza: 75 mg twice daily for 5 days (may be extended in severe infections)
  - Prophylaxis of influenza infection: 75 mg daily
- Pediatrics 1 to 12 years: All doses are twice daily for treatment, once daily for prophylaxis
  - < 16 kg: 30 mg
  - 16–23 kg: 45 mg
  - 24–40 kg: 60 mg
  - > 40 kg: Adult dosing

- Renal dosage adjustment during treatment:
  - CrCl 30–59 ml/min: 30 mg twice daily
  - CrCl 10–29 ml/min: 30 mg once daily
- Renal dose adjustment during prophylaxis
  - CrCl 30–59 ml/min 30 mg once daily
  - CrCl 10–29 ml/min 30 mg every other day

Adverse Reactions: Most Common

Headache, vomiting

Adverse Reactions: Rare/Severe/Important

Neuropsychiatric effects (particularly in children), hypersensitivity including Stevens-Johnson syndrome

Major Drug Interactions

Oseltamivir's Effect on Other Drugs

Oseltamivir may diminish the immunologic effect of the live, attenuated influenza vaccine (nasal vaccine)

Counseling Points

- Oseltamivir is not a substitute for the seasonal influenza vaccine. It should only be used for prophylaxis of influenza in patients who cannot be vaccinated. New formulations of influenza vaccine that are not derived from eggs have decreased the number of patients who cannot be vaccinated.
- The sooner oseltamivir is started, the more effective it is likely to be. It may not help patients who are already recovering from influenza.
- Patients who do not receive the vaccine and contract influenza need to be vaccinated for influenza after they have recovered

Key Points

- Oseltamivir is most effective when started early. Although the package insert says it must be started within 48 hours of symptoms beginning, clinicians often start it later, particularly for severely ill or hospitalized patients.
- Oseltamivir is active against both influenza A and B strains, but dominant strains in the community may be resistant in any given year

ANTIRETROVIRALS, NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

Introduction

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are antiretrovirals used for the treatment of HIV. Currently, it is recommended that antiretroviral regimens contain at least two NRTIs in combination with another class of antiretrovirals, such as a protease inhibitor or an integrase inhibitor in treatment-naïve patients. All NRTIs except abacavir are renally eliminated and require renal dosage adjustments. They also have minimal drug–drug interactions. Mitochondrial toxicities causing lactic acidosis, hepatic steatosis, peripheral neuropathy, pancreatitis, and lipoatrophy are less commonly associated with the NRTIs lamivudine, emtricitabine, abacavir, and tenofovir. Those NRTIs are now the most commonly used agents.

Mechanism of Action for the Drug Class

NRTIs competitively inhibit HIV reverse transcription by causing viral DNA chain termination, preventing viral replication

Members of the Drug Class

In this section: Lamivudine, emtricitabine, tenofovir, abacavir
Others: Didanosine, stavudine, zidovudine

Key Point for the Drug Class

- **Black Box Warning:**
  - Lactic acidosis and severe hepatomegaly with steatosis have been reported with NRTIs.

◉ Lamivudine

Brand Names

Epivir, Epivir HBV, Epzicom (coformulated with abacavir), Combivir (coformulated with zidovudine), Trizivir (coformulated with abacavir and zidovudine), Triumeq (coformulated with abacavir and dolutegravir)

Generic Name

Lamivudine

Rx Only

Dosage Forms

Tablet, oral solution

Usage

HIV infection, chronic hepatitis B

Pregnancy Category C

Dosing

- 300 mg daily or 150 mg twice daily for HIV; 100 mg daily for hepatitis B
- Renal dosage adjustment:
  - CrCl 30–49 ml/min: 150 mg daily
  - CrCl 15–29 ml/min: 150 mg × 1, then 100 mg daily
  - CrCl 5–14 ml/min: 150 mg × 1, then 50 mg daily
  - CrCl < 5 ml/min (including hemodialysis): 50 mg × 1, then 25 mg daily

Adverse Reactions: Most Common

No common reactions

Adverse Reactions: Rare/Severe/Important

Lactic acidosis with hepatic steatosis; severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue lamivudine

Major Drug Interactions

Concomitant administration with emtricitabine should be avoided because they are chemically related (both are cytosine analogs)

Contraindication

Concomitant administration with emtricitabine is contraindicated

Key Points

- **Black Box Warning:**
  - Severe acute exacerbations of hepatitis may occur in HBV-coinfected patients who discontinue lamivudine. Also, HIV testing should be performed before starting lamivudine for HBV since the dose is lower and it may lead to lamivudine-resistant HBV.
- Either lamivudine or emtricitabine is almost always part of combination antiretroviral therapy regimens
- Although well tolerated with minimal toxicity, lamivudine has a low genetic barrier to resistance
- Commonly abbreviated as 3TC

◉ Emtricitabine

Brand Names

Emtriva, Truvada (coformulated with tenofovir disoproxil fumarate), Descovy (coformulated with tenofovir alafenamide)

Generic Name

Emtricitabine

Rx Only

Dosage Forms

Capsule, oral solution

Usage

HIV infection, HIV pre-exposure prophylaxis (when coformulated with tenofovir disoproxil fumarate as Truvada), chronic hepatitis B

Pregnancy Category B

Dosing

- 200 mg capsule daily or 240 mg (24 ml) oral solution daily
- Renal dosage adjustment:
  - CrCl 30–49 ml/min: 200 mg every 2 days (capsule), 120 mg daily (solution)
  - CrCl 15–29 ml/min: 200 mg every 3 days (capsule), 80 mg daily (solution)
  - CrCl < 15 ml/min (including hemodialysis): 200 mg every 4 days (capsule), 60 mg daily (solution), administered after dialysis

Adverse Reactions: Most Common

No common reactions

Adverse Reactions: Rare/Severe/Important

Lactic acidosis with hepatic steatosis; severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue emtricitabine

Major Drug Interactions

Concomitant administration with lamivudine should be avoided because they are chemically related (both are cytosine analogs)

Contraindication

Concomitant administration with lamivudine is contraindicated

Key Points

- **Black Box Warning:**
  - Post-treatment severe acute exacerbations of hepatitis may occur in HBV-coinfected patients who discontinue emtricitabine
- Lamivudine or emtricitabine are almost always part of combination antiretroviral therapy
- Although well tolerated with minimal toxicity, emtricitabine has a low genetic barrier to resistance
- Commonly abbreviated as FTC

◉ Tenofovir Disoproxil Fumarate

Brand Names

Viread, Truvada (coformulated with emtricitabine), Atripla (coformulated with emtricitabine and efavirenz), Complera (coformulated with emtricitabine and rilpivirine), Stribild (coformulated with emtricitabine, cobicistat, and elvitegravir)

Generic Name
Tenofovir disoproxil fumarate

Rx Only

Dosage Forms
Tablet, powder

Usage
HIV infection, HIV pre-exposure prophylaxis (when coformulated with emtricitabine as Truvada), chronic hepatitis B

Pregnancy Category B

Dosing
- Usual dose: 300 mg daily
- Renal dosage adjustment:
  - CrCl 30–49 ml/min: 300 mg every 2 days
  - CrCl 10–29 ml/min: 300 mg every 3 to 4 days
  - CrCl <10 ml/min and not on hemodialysis: no recommendation
  - Hemodialysis: 300 mg daily for 7 days after dialysis

Adverse Reactions: Most Common
Asthenia, headache, nausea, vomiting, diarrhea

Adverse Reactions: Rare/Severe/Important
Nephrotoxicity, decreased bone mineral density, lactic acidosis with hepatic steatosis

Major Drug Interactions
Concurrent use of ledipasvir/sofosbuvir together with tenofovir disoproxil fumarate as part of the elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate combination or with ritonavir-boosted HIV protease inhibitors is not recommended due to increase in tenofovir-associated toxicities

Essential Monitoring Parameters
Renal function (urinalysis every 6 months and serum creatinine every 3 months)

Counseling Point
Adverse effects such as asthenia, headache, nausea, vomiting, and diarrhea should subside in 4 weeks

Key Points
- **Black Box Warning:**
  - Post-treatment severe acute exacerbations of hepatitis may occur in HBV-coinfected patients who discontinue tenofovir disoproxil fumarate.
- Tenofovir disoproxil fumarate and emtricitabine are commonly used in combination antiretroviral therapy
- Avoid the use of tenofovir disoproxil fumarate in patients with baseline renal impairment
- Do not coadminister with adefovir for hepatitis B infection
- Commonly abbreviated as TDF

Tenofovir Alafenamide

Brand Names
Vemlidy, Descovy (coformulated with emtricitabine), Odefsey (coformulated with emtricitabine and rilpivirine), Genvoya (coformulated with emtricitabine, cobicistat, and elvitegravir)

Generic Name
Tenofovir alafenamide

Rx Only

Dosage Forms
Tablet

Usage
HIV infection, chronic hepatitis B

Pregnancy Category B

Dosing
- Usual dose: 25 mg daily in most fixed-dose combinations except with elvitegravir/cobicistat, emtricitabine (10 mg daily)
- Renal dosage adjustment:
  - CrCl < 30 or on hemodialysis: not recommended

Adverse Reactions: Most Common
Headache, nausea, abdominal pain

Adverse Reactions: Rare/Severe/Important
Worsening renal impairment (risk is lower than with tenofovir disoproxil fumarate), lactic acidosis with hepatic steatosis

Major Drug Interactions
Drugs Affecting Tenofovir Alafenamide

Carbamazepine, rifamycins, phenobarbital, St. John's Wort: reduced tenofovir alafenamide concentrations

Essential Monitoring Parameters
Renal function (urinalysis every 6 months and serum creatinine every 3 months)

Counseling Point
Adverse effects, such as headache, nausea, and abdominal pain, should subside in 4 weeks

Key Points
- **Black Box Warning:**
  - Post-treatment severe acute exacerbations of hepatitis may occur in HBV-coinfected patients who discontinue tenofovir alafenamide.
- Tenofovir alafenamide and emtricitabine commonly used in combination antiretroviral therapy
- Do not coadminister with adefovir for hepatitis B infection
- Commonly abbreviated as TAF

◉ Abacavir

Brand Names

Ziagen, Epzicom (coformulated with lamivudine), Triumeq (coformulated with lamivudine and dolutegravir)

Generic Name

Abacavir

Rx Only

Dosage Forms

Tablet, oral solution

Usage

HIV infection

Pregnancy Category C

Dosing

- Usual dose: 600 mg once daily or 300 mg twice daily
- Hepatic dosage adjustment:
  - Child-Pugh Class A: 200 mg twice daily (use oral solution)
  - Child-Pugh Class B or C: contraindicated

Adverse Reactions: Most Common

No common reactions

Adverse Reactions: Rare/Severe/Important

Hypersensitivity reaction (symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, or respiratory symptoms, such as sore throat, cough, or shortness of breath; increased risk if HLA-B*5701 positive), lactic acidosis with hepatic steatosis

Major Drug Interactions

Abacavir's Effect on Other Drugs

- Methadone: Increased clearance, possibly leading to withdrawal
- Ribavirin: Increased risk of lactic acidosis

Essential Monitoring Parameters

Hypersensitivity reaction (fever, rash, nausea, vomiting, malaise or fatigue, or respiratory symptoms, such as sore throat, cough, or shortness of breath)

Contraindications

Any manifestation of a hypersensitivity reaction; patients who test positive for HLA-B*5701 (contraindication). Rechallenging with abacavir after an initial reaction can be fatal and is not recommended.

Counseling Point

Report the following signs/symptoms because they may be associated with a hypersensitivity reaction: fever, rash, nausea, vomiting, malaise or fatigue, or respiratory symptoms, such as sore throat, cough, or shortness of breath

Key Points

- **Black Box Warning:**
  - Severe and possibly fatal hypersensitivity reactions are possible with abacavir. Patients should undergo genetic testing for the presence of the HLA-B*5701 allele before starting; if positive, do not give because it is predictive of hypersensitivity
- Use with caution in patients at high risk of cardiovascular disease; some studies have shown an association between abacavir and an increased risk for myocardial infarction
- Commonly abbreviated as ABC

ANTIRETROVIRALS, NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Introduction

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are antiretrovirals used in the treatment of HIV. They are often used in combination with nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). They tend to have a low genetic barrier to resistance, except for second-generation NNRTIs, such as etravirine and rilpivirine. Etravirine and rilpivirine tend to have fewer adverse effects compared with efavirenz and nevirapine but currently are not preferred agents in treatment-naïve patients. Drug interactions are common because agents in this class are substrates, as well as inducers and inhibitors, of the CYP3A4 enzyme system.

Mechanism of Action for the Drug Class

NNRTIs inhibit the essential viral enzyme reverse transcriptase in a noncompetitive manner, preventing viral replication

Members of the Drug Class

In this section: Efavirenz, rilpivirine
Others: Nevirapine, etravirine

◉ Efavirenz

Brand Names

Sustiva, Atripla (coformulated with tenofovir disoproxil fumarate and emtricitabine)

Generic Name
Efavirenz

Rx Only

Dosage Forms
Capsule, tablet

Usage
HIV infection

Pregnancy Category D

Dosing
- 600 mg daily on an empty stomach
- Use with caution in patients with hepatic impairment

Adverse Reactions: Most Common
Dizziness, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, hallucinations, rash

Adverse Reactions: Rare/Severe/Important
Grade 3 or 4 rash (has rarely progressed to Stevens-Johnson syndrome)

Major Drug Interactions
CYP3A4 substrate and moderate inducer

Medications That Should Not Be Administered with Efavirenz

Other NNRTIs, oral midazolam, triazolam, voriconazole (at standard doses), elbasvir/grazoprevir, dasabuvir plus paritaprevir/ombitasvir/ritonavir, simeprevir, St. John's Wort, and avanafil

Drugs Affecting Efavirenz

Inducers of CYP450 3A4 lower efavirenz concentrations
Inhibitors of CYP450 3AR increase efavirenz concentrations

Essential Monitoring Parameters
Liver function tests every 3 months, lipid panel yearly (if normal)

Contraindications
Concomitant administration with other NNRTIs, oral midazolam, triazolam, voriconazole (at standard doses), elbasvir/grazoprevir, dasabuvir plus paritaprevir/ombitasvir/ritonavir, simeprevir, St. John's Wort, and avanafil

Counseling Point
Take on an empty stomach at bedtime

Key Points
- Avoid in women of childbearing potential because efavirenz should be used with caution in the first trimester of pregnancy
- Avoid in patients with unstable psychiatric disease due to adverse CNS effects
- Commonly abbreviated as EFV

Rilpivirine

Brand Names
Edurant, Complera (coformulated with tenofovir disoproxil fumarate and emtricitabine), Odefsey (coformulated with tenofovir alafenamide and emtricitabine)

Generic Name
Rilpivirine

Rx Only

Dosage Forms
Tablet

Usage
HIV infection

Pregnancy Category B

Dosing
- 25 mg daily with a high-calorie meal
- Hepatic dosage adjustment:
  - Child-Pugh Class A, B, or C: No dosage adjustment recommended; use with caution

Adverse Reactions: Most Common
Depressive disorders, headache, insomnia, and rash

Adverse Reactions: Rare/Severe/Important
Grade 3 or 4 rash (has rarely progressed to Stevens-Johnson syndrome)

Major Drug Interactions
CYP3A4 substrate

Medications That Should Not Be Administered with Rilpivirine

Other NNRTIs, proton pump inhibitors, carbamazepine, phenobarbital, phenytoin, oxcarbazepine, rifampin, rifapentine, dexamethasone, St. John's Wort, Avanafil

Drugs Affecting Rilpivirine

H2-receptor antagonists may decrease concentrations of rilpivirine. Separate by at least 12 hours before or at least 4 hours after.
Inhibitors of CYP3A4 increase rilpivirine concentrations

Essential Monitoring Parameters
Liver function tests every 3 months, lipid panel yearly (if normal)

Contraindications

Concomitant administration with other NNRTIs, proton pump inhibitors

Counseling Point

Take with a high-calorie meal

Key Points

- Avoid proton pump inhibitors (contraindicated), H2- receptor antagonists are okay to use if separated by at least 12 hours before or at least 4 hours after
- Commonly abbreviated as RPV

ANTIRETROVIRALS, PROTEASE INHIBITORS

Introduction

The protease inhibitors (PIs) are antiretrovirals used in the treatment of HIV. They are often used in combination with nucleoside/nucleotide reverse transcriptase inhibitors. Most PIs have low oral bioavailability due to hepatic first-pass metabolism. As a result, PIs must be given with ritonavir or cobicistat to pharmacokinetically "boost" levels of the primary PI. Drugs in this class have a high genetic barrier to resistance. Most are substrates and inhibitors of the CYP450 enzyme system and can cause clinically significant drug–drug interactions. PIs are often associated with adverse effects, such as gastrointestinal intolerance, lipodystrophy, glucose intolerance, and dyslipidemia.

Mechanism of Action for the Drug Class

Inhibit the essential viral enzyme protease, preventing viral maturation

Members of the Drug Class

In this section: Atazanavir, darunavir
Others: lopinavir/ritonavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir

◉ Darunavir

Brand Name

Prezista, Prezcobix (coformulated with cobicistat)

Generic Name

Darunavir

Rx Only

Dosage Form

Tablet

Usage

HIV infection

Pregnancy Category C

Dosing

- Treatment-naïve or treatment-experienced patients with no darunavir resistance–associated mutations: Darunavir 800 mg + ritonavir 100 mg daily with food
- Treatment-experienced patients with at least one darunavir resistance–associated mutation: Darunavir 600 mg + ritonavir 100 mg twice daily with food
- Darunavir coformulated with cobicistat: one tablet daily with food
- Hepatic dosage adjustments: If severe hepatic impairment, use is not recommended

Adverse Reactions: Most Common

Diarrhea, nausea, vomiting, rash, headache, abdominal pain

Adverse Reactions: Rare/Severe/Important

Hypersensitivity

Major Drug Interactions

Major CYP3A4 substrate

Medications That Should Not Be Administered with Darunavir

Simvastatin, lovastatin, rifampin, rifapentine, oral midazolam, triazolam, phenobarbital, phenytoin, fluticasone

Drug Interactions with Darunavir That May Require Dosage Adjustment or Monitoring

Many, due to inhibition of CYP3A4 metabolism

Essential Monitoring Parameters

Liver function tests every 3 months, lipid panel yearly (if normal)

Counseling Points

- Gastrointestinal discomfort is likely during the initiation of therapy but may subside within 4 weeks
- Take with food to decrease gastrointestinal side effects and for increased absorption of the drug

Key Points

- Use caution in patients with sulfa allergies due to sulfa moiety in darunavir
- Do not give without a booster
- May be boosted by either ritonavir or cobicistat
- Commonly abbreviated as DRV

◉ Atazanavir

Brand Name

Reyataz, Evotaz (coformulated with cobicistat)

Generic Name

Atazanavir

Rx Only

Dosage Form

Capsule, tablet

Usage

HIV infection

Pregnancy Category B

Dosing

- Boosted or treatment-experienced patients or with tenofovir: Atazanavir 300 mg + ritonavir 100 mg once daily with food
- Unboosted and PI-naïve patients: Atazanavir 400 mg once daily with food (not recommended)
- Atazanavir coformulated with cobicistat: 1 tablet daily with food
- Hepatic dosage adjustment:
  - Child-Pugh Class B: Atazanavir 300 mg daily without boosting
  - Child-Pugh score Class C: Not recommended

Adverse Reactions: Most Common

Nausea, jaundice/scleral icterus, rash, headache, abdominal pain, vomiting, diarrhea

Adverse Reactions: Rare/Severe/Important

Nephrolithiasis, PR interval prolongation

Major Drug Interactions

Major CYP3A4 substrate

Medications That Should Not Be Administered with Atazanavir

Simvastatin, lovastatin, rifampin, rifapentine, oral midazolam, triazolam, phenobarbital, phenytoin, fluticasone

Drug Interactions with Atazanavir That May Require Dosage Adjustment or Monitoring

Many, due to inhibition of CYP450 metabolism

Drugs affecting Atazanavir

- Acid-reducing agents: Drug-regimen modification is required due to the need for gastric acidity to absorb atazanavir. Specific recommendations are available and differ between acid-reducing agents and the level of treatment experience of the patient.

Essential Monitoring Parameters

Liver function tests and total bilirubin every 3 months, lipid panel yearly (if normal)

Counseling Points

- Gastrointestinal discomfort is likely during the initiation of therapy but may subside within 4 weeks
- Take with food and drink plenty of water
- Do not take antacids without first talking to your physician
- You may notice that the color of your skin and eyes turns yellow; talk to your physician

Key Points

- Use with caution in patients taking acid-reducing agents. Many of those agents are overused, and it may be possible to discontinue them.
- Not recommended to be given without a booster
- May be boosted by either ritonavir or cobicistat
- Commonly abbreviated as ATV

PHARMACOKINETIC ENHANCERS

Introduction

Pharmacokinetic enhancers are often called "boosters" since they are used in the treatment of HIV for the sole purpose of "boosting" protease inhibitor drug concentrations. It is recommended that all protease inhibitors be used with a pharmacokinetic enhancer.

Mechanism of Action for the Drug Class

Those agents inhibit CYP3A4, which thereby increases the systemic exposure of protease inhibitors and other CYP3A4 substrates

Members of the Drug Class

In this section: Ritonavir, cobicistat

Ritonavir

Brand Names

Norvir, Kaletra (coformulated with lopinavir)

Generic Name

Ritonavir

Rx Only

Dosage Forms

Capsule, tablet, oral solution

Usage

Used as a pharmacokinetic "booster" to protease inhibitors

Pregnancy Category B

Dosing

Usual dose (as a pharmacokinetic "booster"): 100 mg daily with the protease inhibitor (100 mg twice daily if protease inhibitor given twice daily)

Adverse Reactions: Most Common

Nausea, vomiting, diarrhea, abdominal pain

Major Drug Interactions

Medications That Should Not Be Administered Concomitantly with Ritonavir

Simvastatin, lovastatin, cisapride, pimozide, oral midazolam, triazolam, ergot alkaloids, amiodarone, flecainide, propafenone, quinidine, rifampin, St. John's wort, fluticasone

Drug Interactions with Ritonavir That May Require Dosage Adjustment or Monitoring

Many, due to inhibition of CYP450 metabolism

Counseling Points

- Gastrointestinal discomfort is likely during the initiation of therapy but may subside within 4 weeks
- Take with food to decrease gastrointestinal side effects

Key Points

- Ritonavir is no longer used as a primary PI due to low tolerance at effective doses but is frequently used as a pharmacokinetic "booster" for other PIs via inhibition of the CYP450 system
- Commonly abbreviated as RTV, or "/r" in combination regimens

Cobicistat

Brand Names

Tybost, Prezcobix (coformulated with darunavir), Evotaz (coformulated with atazanavir), Stribild (coformulated with elvitegravir, emtricitabine, tenofovir disoproxil fumarate), Genvoya (coformulated with elvitegravir, emtricitabine, tenofovir alafenamide)

Generic Name

Cobicistat

Rx Only

Dosage Forms

Tablet

Usage

Used as a pharmacokinetic "booster," primarily with the agents atazanavir, darunavir, and elvitegravir

Pregnancy Category: Not Categorized

Dosing

Usual dose: 150 mg daily with concomitant atazanavir, darunavir, or elvitegravir

Adverse Reactions: Most Common

Rash, liver function test elevations

Major Drug Interactions

Medications That Should Not Be Administered Concomitantly with Cobicistat

Simvastatin, lovastatin, cisapride, pimozide, oral midazolam, triazolam, ergot alkaloids, amiodarone, flecainide, propafenone, quinidine, rifampin, St. John's wort, fluticasone

Drug Interactions with Cobicistat That May Require Dosage Adjustment or Monitoring

Many, due to inhibition of CYP450 metabolism

Essential Monitoring Parameters

When coadministered with tenofovir disoproxil fumarate, renal function should be monitored every 3 months

Counseling Point

Take with food

Key Points

- Cobicistat is a pharmacokinetic enhancer than can only be used to boost darunavir, atazanavir, and elvitegravir. Use as a booster with other protease inhibitors has not be studied.
- Commonly abbreviated as COBI, or "/c" in combination regimens

ANTIRETROVIRALS, INTEGRASE STRAND TRANSFER INHIBITORS

Introduction

Integrase inhibitors are antiretrovirals used in the treatment of HIV. They are often used in combination with NRTIs. Compared with the PIs and NNRTIs, integrase inhibitors are extremely well tolerated and have limited adverse effects.

Mechanism of Action for the Drug Class

Integrase inhibitors inhibit the essential viral enzyme integrase, preventing integration of the proviral gene into host DNA

Members of the Drug Class

In this section: Dolutegravir, raltegravir, elvitegravir

◉ Dolutegravir

Brand Name

Tivicay, Triumeq (coformulated with abacavir and lamivudine)

Generic Name

Dolutegravir

Rx Only

Dosage Form

Tablet

Usage

HIV infection

Pregnancy Category: Not Categorized

Dosing

- 50 mg daily for treatment-naïve patients
- 50 mg twice daily for patients with suspected or documented integrase mutation
- Hepatic dosing adjustment: Use with caution in cases of severe hepatic impairment

Adverse Reactions: Most Common

Insomnia, headache

Adverse Reactions: Rare/Severe/Important

None

Major Drug Interactions

Drugs Affecting Dolutegravir

Polyvalent cations (aluminum, magnesium, calcium–containing antacids) lower dolutegravir concentrations. Administer 2 hours after or 6 hours before

Dolutegravir's Effect on Other Drugs

Increased concentrations of metformin occur—limit metformin dose to no more than 1000 mg per day

Do not coadminister with: rifampin, rifapentine, dofetilide, St. John's Wort

Counseling Points

- Separate administration with antacids or multivitamins, which contain polyvalent cations.
- Take in the morning if experiencing insomnia when taking it at nighttime.

Key Point

Dolutegravir is very well tolerated with minimal drug interactions and has a high genetic barrier to resistance, which is why this is a good agent for many patients, both treatment naïve and treatment experienced.

◉ Raltegravir

Brand Name

Isentress

Generic Name

Raltegravir

Rx Only

Dosage Form

Tablet

Usage

HIV infection

Pregnancy Category C

Dosing

- 400 mg twice daily
- Concomitant administration with rifampin: 800 mg twice daily
- Hepatic dosing adjustment: Use with caution in cases of severe hepatic impairment

Adverse Reactions: Most Common

Insomnia, headache, dizziness, nausea, fatigue

Adverse Reactions: Rare/Severe/Important

Hypersensitivity rash, Stevens–Johnson syndrome, and toxic epidermal necrolysis

Major Drug Interactions

Drugs Affecting Raltegravir

Polyvalent cations (aluminum, magnesium, calcium-containing antacids) lower raltegravir concentrations. Administer 2 hours after or 6 hours before.

Counseling Point

Separate administration with antacids or multivitamins, which contain polyvalent cations.

Key Point

Although well tolerated with minimal drug interactions, raltegravir has a low genetic barrier to resistance.

⦿ Elvitegravir

Brand Name

Vitekta (discontinued), Stribild (coformulated with cobicistat, emtricitabine, tenofovir disoproxil fumarate), Genvoya (coformulated with cobicistat, emtricitabine, tenofovir alafenamide)

Generic Name

Elvitegravir

Rx Only

Dosage Form

Tablet

Usage

HIV infection

Pregnancy Category B

Dosing

- 150 mg daily, always coformulated with cobicistat, emtricitabine, tenofovir disoproxil fumarate or tenofovir alafenamide
- Hepatic dosing adjustment: Use with caution in cases of severe hepatic impairment
- Renal dosing adjustment:
  - Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate should not be initiated in patients with CrCl < 70 ml/min; discontinue if CrCl declines to < 50 ml/min while patient is on therapy
  - Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide is not recommended for use in patients with CrCl < 30 ml/min

Adverse Reactions: Most Common

Diarrhea

Adverse Reactions: Rare/Severe/Important

None

Major Drug Interactions

Drugs Affecting Elvitegravir

Polyvalent cations (aluminum, magnesium, calcium-containing antacids) lower elvitegravir concentrations. Administer 2 hours after or 6 hours before

Many more drug interactions since elvitegravir is always coformulated with cobicistat; all cobicistat drug interactions apply.

Counseling Point

Separate administration with antacids or multivitamins, which contain polyvalent cations.

Key Point

Elvitegravir is generally well tolerated and has a low genetic barrier to resistance and since it is always coformulated with cobicistat, there are many associated drug-drug interactions.

ANTIHEPACIVIRAL (ANTI-HCV)

Introduction

Direct-acting antiviral oral combination regimens are recommended in the treatment of HCV. Currently, there are several direct-acting antiviral oral combinations to select from based on HCV-genotype, patient-specific factors, and comorbid conditions. Each combination differs in the genotypes they are active against, drug-drug interactions and adverse effects. Currently, these medications are very expensive so adherence is very important.

Mechanisms of Action for the Drug Class

Direct-acting antivirals are typically given as coformulated combination regimens. Each component has a different mechanism of action that targets different sites in the HCV life cycle to inhibit replication: there are NS3/4A protease inhibitors, NS5B polymerase inhibitors, and NS5A protein inhibitors.

Key Point for the Drug Class

- **Black Box Warning:**
  - Reactivation of hepatitis B viral infection can occur with treatment of direct-acting, antihepatitis C medications. Test all patients for HBV infection before beginning therapy.

Members of the Drug Class

In this section: ledipasvir/sofosbuvir, elbasvir/grazoprevir

Others: daclatasvir, ombitasvir/paritaprevir/ritonavir, ombitasvir/paritaprevir/ritonavir/dasabuvir, simeprevir, sofosbuvir, sofosbuvir/velpatasvir

⦿ Ledipasvir/Sofosbuvir

Brand name

Harvoni

Generic name
Ledipasvir/sofosbuvir

Rx Only

Dosage forms
Tablet

Usage
Hepatitis C virus infection genotypes 1, 4, 5, or 6

Pregnancy Category
No human data—animal data suggest low risk (contraindicated if given with ribavirin)

Dosing
Adults: 1 tablet daily (fixed dose tablet: 90 mg ledipasvir and 400 mg sofosbuvir)
Renal dosage adjustment: Avoid if CrCl < 30 ml/min

Adverse Reactions: Most Common
Headache, fatigue, weakness

Adverse Reactions: Rare/Severe/Important
Hepatitis B virus infection reactivation

Major Drug Interactions
Drugs Affecting Ledipasvir/Sofosbuvir

Rifampin: decrease ledipasvir/sofosbuvir concentrations
Antacids, H_2-receptor antagonists, and proton-pump inhibitors: decrease ledipasvir/sofosbuvir concentrations

Ledipasvir/Sofosbuvir Effects on Other Drugs

Amiodarone: serious symptomatic bradycardia
Tenofovir: increased tenofovir concentrations

Counseling Points
- Do not take an antacid that has aluminum or magnesium within 4 hours of this drug
- Do not start taking an acid-suppression medication during treatment

Key Points
- Coadministration with amiodarone may result in serious symptomatic bradycardia and is not recommended
- Acid-reducing agents decrease the concentration of ledipasvir/sofosbuvir
- Sofosbuvir/velpatasvir (Epclusa) is similar to ledipasvir/sofosbuvir but can be used in HCV genotypes 1, 2, 3, 4, 5, or 6

◉ Elbasvir/Grazoprevir

Brand name
Zepatier

Generic name
Elbasvir/grazoprevir

Rx Only

Dosage forms
Tablet

Usage
Hepatitis C virus infection genotypes 1 or 4

Pregnancy Category
No human data—adverse events were not observed in animal reproductive studies

Dosing
Adults: 1 tablet daily (fixed dose tablet: 50 mg elbasvir and 100 mg grazoprevir)
Hepatic dosage adjustment: contraindicated in Child-Pugh class B or C

Adverse Reactions: Most Common
Headache, fatigue, nausea

Major Drug Interactions
Drugs Affecting Elbasvir/Grazoprevir

Phenytoin, rifampin, carbamazepine: decrease the concentrations of *elbasvir/grazoprevir*
Darunavir, atazanavir, cyclosporine: Increase risk of ALT elevations

Elbasvir/Grazoprevir Effects on Other Drugs

HMG-CoA Reductase Inhibitors: increase concentrations and risk of myopathy
Tacrolimus: increase concentrations

Counseling Points
- Keep in the original blister pack until time of use
- Take at the same time every day

Key Points
- Elbasvir/grazoprevir can be used in patients with any degree of renal impairment, including patients receiving hemodialysis
- Elbasvir/grazoprevir is contraindicated in moderate to severe hepatic impairment
- Elbasvir/grazoprevir is contraindicated with some drugs. Always check for drug interactions before beginning therapy.

REVIEW QUESTIONS

1. Which of the following drugs interacts with alcohol to produce a disulfiram-like reaction?
   a. Amoxicillin
   b. Flagyl
   c. Doxycycline
   d. Clindamycin

2. Which of the following drugs only has one approved indication: treatment of uncomplicated urinary tract infection?
   a. Biaxin
   b. Trimethoprim/sulfamethoxazole
   c. Nitrofurantoin
   d. Rifampin

3. Which of the following drugs are known to cause rhabdomyolysis?
   a. Cefpodoxime
   b. Zithromax
   c. Avelox
   d. Daptomycin

4. Which of the following drugs can be given as a single IV infusion for the treatment of skin and skin-structure infection?
   a. Vancomycin
   b. Oritavancin
   c. Cubicin
   d. Clindamycin

5. Which of the following drugs may prolong the QTc interval, especially when administered with other drugs that prolong the QTc?
   a. Clarithromycin
   b. Clindamycin
   c. Ampicillin
   d. Minocycline

6. Which of the following drugs may be administered either orally or IV for the treatment of invasive aspergillosis?
   a. Diflucan
   b. Isoniazid
   c. Amphotericin B
   d. Vfend

7. Which of the following treatment indications is oseltamivir used for?
   a. Genital herpes
   b. Urinary tract infection
   c. Influenza
   d. Hepatitis C virus

8. Which of the following drugs have a very long half-life, allowing short-course therapy for many indications?
   a. Azithromycin
   b. Cefuroxime
   c. Vancomycin
   d. Zovirax

9. Which of the following drugs has a warning for tendon rupture and CNS toxicities?
   a. Linezolid
   b. Piperacillin-tazobactam
   c. Tobramycin
   d. Levofloxacin

10. Which of the following drugs is a strong CYP3A4 inducer?
    a. Linezolid
    b. Rifampin
    c. Azithromycin
    d. Levofloxacin

11. Which of the following drugs can cause oto-toxicity and nephrotoxicity?
    a. Tetracycline
    b. Amikacin
    c. Metronidazole
    d. Daptomycin

12. Which of the following drugs should be avoided with ledipasvir/sofosbuvir?
    a. Digoxin
    b. Metoprolol
    c. Amiodarone
    d. Simvastatin

13. Which of the following drugs should be avoided in combination with serotonin modulators?
    a. Linezolid
    b. Daptomycin
    c. Vancomycin
    d. Clindamycin

14. Which of the follow is a common side effect of atazanavir?
    a. Insomnia
    b. Dizziness
    c. Scleral icterus
    d. Renal toxicity

15. Which of the following integrase strand transfer inhibitors have a drug-drug interaction with metformin?

- **a.** Raltegravir
- **b.** Dolutegravir
- **c.** Darunavir
- **d.** Elvitegravir

16. Which of the follow nucleoside/nucleotide reverse transcriptase inhibitors requires hepatic dose adjustments?

- **a.** Lamivudine
- **b.** Emtricitabine
- **c.** Tenofovir disoproxil fumarate
- **d.** Abacavir

17. Before initiating darunavir, what must be verified before starting?

- **a.** Sulfa allergy status
- **b.** HLA B*5701 status
- **c.** Renal function
- **d.** Patient weight

18. What is a common side effect of all protease inhibitors?

- **a.** Depression
- **b.** Gastrointestinal upset
- **c.** Kidney dysfunction
- **d.** Insomnia

19. Which antiretroviral agent cannot be used with proton pump inhibitors?

- **a.** Efavirenz
- **b.** Dolutegravir
- **c.** Rilpivirine
- **d.** Abacavir

20. Which antiretroviral agent has the fewest drug-drug interactions?

- **a.** Atazanavir
- **b.** Efavirenz
- **c.** Darunavir
- **d.** Raltegravir

21. Which antiretroviral agent should be taken on an empty stomach at bedtime?

- **a.** Rilpivirine
- **b.** Efavirenz
- **c.** Elvitegravir
- **d.** Lamivudine

22. Which one of the following medications cause a class drug interaction with all integrase strand transfer inhibitors?

- **a.** Polyvalent cations
- **b.** Proton pump inhibitors
- **c.** H2 receptor antagonists
- **d.** Warfarin

23. Which of the following falsely elevates coagulation tests and its concomitant use with heparin is contraindicated?

- **a.** Vancomycin
- **b.** Dalbavancin
- **c.** Orbactiv
- **d.** Clindamycin

24. Which of the following inhibits two sequential steps in the folate-synthesis pathway, ultimately inhibiting DNA synthesis?

- **a.** Piperacillin–tazobactam
- **b.** Bactrim
- **c.** Unasyn
- **d.** Valtrex

25. Which of the following requires premedication with diphenhydramine and acetaminophen as well as IV fluids before administration?

- **a.** Voriconazole
- **b.** Diflucan
- **c.** Vancomycin
- **d.** AmBisome

26. Which of the following is recommended for the treatment of Gonorrhea?

- **a.** Cefdinir
- **b.** Levofloxacin
- **c.** Ceftriaxone
- **d.** Amoxicillin

27. Which of the following antibiotics treats infections caused by *Pseudomonas aeruginosa*?

- **a.** Ceftriaxone
- **b.** Moxifloxacin
- **c.** Linezolid
- **d.** Piperacillin–tazobactam

28. Which of the following is a topical antibiotic used in the treatment of minor skin infections?

- **a.** Gentamicin
- **b.** Neomycin/polymyxin B
- **c.** Ciprofloxacin
- **d.** Amoxil

29. Which of the following is a first-generation cephalosporin?

- **a.** Ceftaroline
- **b.** Cefzil
- **c.** Omnicef
- **d.** Keflex

30. Which of the following should not be used in a urinary tract infection?

- **a.** Bactrim
- **b.** Avelox
- **c.** Levofloxacin
- **d.** Cipro

CHAPTER 4

Antineoplastics

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ALKYLATING AGENTS

Introduction

Alkylating agents are a large drug class of chemotherapeutic agents composed of drugs used in adults and children to treat a number of malignant and nonmalignant diseases. The most notable side effects include bone marrow suppression, nausea and vomiting, and mucositis, as well as long-term complications, such as sterility and secondary malignancies. Those drugs have a wide dosing range based on the indication and route of administration.

Mechanism of Action for the Drug Class

Alkylating agents form strong covalent bonds with DNA, inhibiting replication and causing bond breaks and cell death. Those agents are toxic to DNA and are considered cell-cycle nonspecific, meaning that they can cause cell death, regardless of the phase of cell division.

Members of the Drug Class

In this section: Cyclophosphamide, temozolomide
Others: Altretamine, bendamustine, busulfan, carmustine, chlorambucil, dacarbazine, ifosfamide, lomustine, mechlorethamine, melphalan, procarbazine, streptozocin, thiotepa

◉ Cyclophosphamide

Brand Name
Cytoxan

Generic Name
Cyclophosphamide

Rx Only

Dosage Forms
Injection, capsule

Usage

- *Oncologic: Hodgkin's and non-Hodgkin's lymphoma, chronic lymphocytic leukemia (CLL), acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL),* multiple myeloma, neuroblastoma, breast cancer, testicular cancer, ovarian cancer, lung cancer, stem cell immobilization, Ewing sarcoma, rhabdomyosarcoma, mycosis fungoides, Waldenstrom macroglobulinemia, Wilms' tumor
- Nononcologic: Severe rheumatoid disorders, Wegener's granulomatosis, myasthenia gravis, multiple sclerosis, systemic lupus erythematosus, refractory Juvenile idiopathic arthritis, lupus nephritis, autoimmune hemolytic anemia, idiopathic thrombocytic purpura (ITP), antibody-induced pure red cell aplasia, nephrotic syndrome in children, uveitis, recurrent pericarditis

Pregnancy Category D

Dosing

- Individual protocols specify dosing for specific indications and institutions
- Usual doses:
  - Oral: 50–100 mg/m^2 per day up to 14 days continuous therapy or 1–5 mg/kg/day
  - IV: Single dose of 400–1800 mg/m^2, which may be repeated at 2– to 4–week intervals
- High dose: 1.8 g/m^2 IV daily for 4 days (total of 7.2 g/m^2) or 50 mg/kg daily for 4 days
- Renal dosage adjustment:
  - CrCl < 10 ml/min: Administer 75% of normal dose
  - Hemodialysis: Administer 50% of dose post hemodialysis
- Hepatic dosage adjustment:
  - Bilirubin 3.1–5 mg/dl or transaminases > 3 times the upper limit of normal: Administer 75% of dose
  - Bilirubin > 5 mg/dl: Avoid use

Adverse Reactions: Most Common

Leukopenia, nausea and vomiting, alopecia, diarrhea, mucositis, amenorrhea

Adverse Reactions: Rare/Severe/Important

Hemorrhagic cystitis, sterility, infertility, secondary malignancies, SIADH, cardiac necrosis, renal tubular necrosis, skin rash

Major Drug Interactions

Drugs Affecting Cyclophosphamide

Antineoplastics: Enhance bone marrow suppression

Cyclophosphamide's Effect on Other Drugs

- Succinylcholine: Decreases metabolism
- Vaccines: Diminishes therapeutic effect of vaccines via immunosuppression

Contraindications

Severely depressed bone marrow function, urinary outflow obstruction

Counseling Points

- Drink plenty of fluids (3–4 l daily) for at least 24 hours after an IV dose
- Report any painful urination or discolored or bloody urine
- Take oral doses early in the day

Key Points

- Doses >1 g/m^2 are likely to require uroprotection with Mesna to prevent hemorrhagic cystitis
- Monitor patients for signs of leukopenia and infection
- Give patient antiemetics to prevent nausea and vomiting

◉ Temozolomide

Brand Name

Temodar

Generic Name

Temozolomide

Rx Only

Dosage Forms

Capsule, injection

Usage

Malignant glioblastoma, refractory anaplastic astrocytoma

Pregnancy Category D

Dosing

- Anaplastic astrocytoma (refractory): Oral, IV:
  - Initial dose: 150 mg/m^2 daily for 5 days; repeat every 28 days
  - Subsequent doses: 100–200 mg/m^2 daily for 5 days per treatment cycle
- Glioblastoma multiforme (newly diagnosed, high-grade glioma): Oral, IV:
  - Concomitant phase: 75 mg/m^2 daily for 42 days with focal radiotherapy
  - Maintenance phase: Begin 4 weeks after concomitant phase completion.
    - Cycle 1: 150 mg/m^2/day for 5 days and repeat every 28 days
    - Cycles 2–6: 100–200 mg/m^2/day for 5 days every 28 days
- Renal dosage adjustment: If CrCl < 36 ml/min/m^2, use with caution

Adverse Reactions: Most Common

Leukopenia, anemia, alopecia, nausea, headaches

Adverse Reactions: Rare/Severe/Important

Pancytopenia, Stevens-Johnson syndrome, severe life-threatening opportunistic infections, pneumonitis

Major Drug Interactions

Drugs Affecting Temozolomide

- Clozapine: Increases risk of agranulocytosis
- Valproic acid: Increases toxicity

Temozolomide's Effects on Other Drugs

- Vaccines: Efficacy may be diminished

Contraindications

Hypersensitivity to temozolomide or dacarbazine, severely depressed bone marrow function

Counseling Points

- Swallow capsules whole with a glass of water; do not chew or open the capsules
- The incidence of nausea and vomiting is decreased when taken on an empty stomach and/or at bedtime
- Take capsules consistently either with food or without food (absorption is affected by food)

Key Points

- *Pneumocystis carinii* pneumonia (PCP) prophylaxis should be given concurrently with radiation
- No live virus vaccines should be given during therapy
- Antiemetics should be given to prevent nausea and vomiting
- Increased MGMT (O-6-methylguanine-DNA methyltransferase) activity/levels within tumor tissue is associated with temozolomide resistance

ANTHRACYCLINES

Introduction

Anthracyclines are a group of antineoplastic drugs used to treat a variety of malignant diseases, including both hematologic and solid tumors. Most anthracyclines, with the exception of valrubicin, are administered intravenously and most notable for causing cardiotoxicity. The anthracyclines administered intravenously are vesicants that can cause severe skin necrosis if extravasation occurs.

Mechanism of Action for the Drug Class

Inhibit DNA and RNA synthesis by intercalation of DNA base pairs and inhibition of DNA repair by topoisomerase.

Members of the Drug Class

In this section: Doxorubicin
Others: Daunorubicin, epirubicin, idarubicin, mitoxantrone, valrubicin

◉ Doxorubicin

Brand Name

Adriamycin

Generic Name

Doxorubicin

Rx Only

Dosage Form

Injection

Usage

Acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), Hodgkin's disease, *malignant lymphoma,* soft tissue and bone sarcomas, thyroid cancer, small cell lung cancer, *breast cancer,* gastric cancer, ovarian cancer, bladder cancer, neuroblastoma, Wilms' tumor, multiple myeloma

Pregnancy Category D

Dosing

- Individual protocols specify dosing for specific indications and institutions
- Children:
  - 30–75 mg/m^2 per dose every 3 to 4 weeks *or*
  - 20–30 mg/m^2 per dose once weekly *or*
  - 60–90 mg/m^2 given as a continual infusion over 96 hours every 3 to 4 weeks
- Adults:
  - 60–75 mg/m^2 per dose every 3 to 4 weeks *or*
  - 20–30 mg/m^2 daily for 3 days every 4 weeks *or*
  - 60 mg/m^2 per dose every 2 weeks (dose dense)
- Hepatic dosage adjustment:
  - Transaminases 2 to 3 times the upper limit of normal: Administer 75% of dose
  - Bilirubin 1.2–3 mg/dl or transaminases > 3 times the upper limit of normal: Administer 50% of dose
  - Bilirubin 3.1–5 mg/dl: Administer 25% of dose
  - Bilirubin > 5 mg/dl or Child Pugh Class C: Do not administer

Adverse Reactions: Most Common

Leukopenia, anemia, thrombocytopenia, nausea and vomiting, alopecia, diarrhea, mucositis, amenorrhea

Adverse Reactions: Rare/Severe/Important

Acute and delayed cardiotoxicity, sterility, secondary malignancy

Major Drug Interactions

Drugs Affecting Doxorubicin

- Cyclosporine: May increase doxorubicin levels
- Paclitaxel: Reduces the clearance of doxorubicin
- Trastuzumab: May increase cardiotoxicity of doxorubicin

Doxorubicin's Effect on Other Drugs

- Digoxin: Levels may be decreased
- Phenytoin: Levels may be decreased
- Radiation: Severe skin reactions are possible

Contraindications

Recent myocardial infarction, severe myocardial insufficiency, severe arrhythmia; previous therapy with high cumulative doses of doxorubicin, daunorubicin, idarubicin, or other anthracyclines and anthracenediones; baseline neutrophil count < 1500/mm^3; severe hepatic impairment

Counseling Points

- This drug may darken urine for 24 to 48 hours
- Watch for fever, malaise, sore mouth or throat, pain or swelling at injection site

Key Points

- Dose adjustments may be needed for patients with inadequate marrow reserve
- No live virus vaccines should be given during therapy

- Doxorubicin is a vesicant. Extravasation should be treated with topical dimethylsulfoxide (DMSO) and cold compresses or dexrazoxane.
- Patients should have ejection fraction measured before starting, during, and after therapy
- Monitor patients for signs of infection and mucositis
- Premedicate with antiemetics to prevent nausea and vomiting
- A liposomal formulation of doxorubicin (Doxil, Lipodox 50) is available. However, note that the two formulations have different indications and dosing regimens and cannot be substituted for each other.

ANTIANDROGENS

Introduction

Antiandrogens represent a class of drugs used in the management of prostate cancer that either interfere with the production of androgens or prevent androgens from working properly. Testosterone is the primary androgen that stimulates growth of prostate cancer cells.

Mechanism of Action for the Drug Class

Antiandrogens, such as bicalutamide, are nonsteroidal, competitive, androgen receptor antagonists that block the binding of testosterone. Abiraterone acetate selectively and irreversibly inhibits the CYP17 enzyme responsible for androgen biosynthesis.

Members of the Drug Class

In this section: Abiraterone acetate, bicalutamide
Others: cyproterone, enzalutamide, flutamide, nilutamide

◉ Abiraterone acetate

Brand Name

Zytiga

Generic Name

Abiraterone acetate

Rx Only

Dosage Forms

Tablet

Usage

Metastatic castration-resistant prostate cancer

Pregnancy Category X

Dosing

- Oral: 1000 mg once daily (in combination with prednisone 5 mg twice daily)
- Hepatic dosage adjustment:
  - Moderate (Child-Pugh class B) prior treatment initiation: 250 mg once daily; permanently discontinue if transaminases > 5 times the upper limit of normal or total bilirubin > 3 times the upper limit of normal during treatment
  - Severe (Child-Pugh class C) prior treatment initiation: Avoid use

Adverse Reactions: Most Common

Fatigue, hypertriglyceridemia, hyperglycemia, hypernatremia, hypophosphatemia, hot flashes, joint swelling, myalgias, diarrhea, dyspnea, mineralocorticoid excess (fluid retention, hypertension, hypokalemia)

Adverse Reactions: Rare/Severe/Important

Hepatotoxicity, adrenocortical insufficiency

Major Drug Interactions

Drugs affecting Abiraterone acetate

- Strong CYP3A4 inducers: Decreases serum concentration
- Spironolactone: Diminishes therapeutic effect

Abiraterone acetate's Effect on Other Drugs

- Clozapine: Increases serum concentration
- Metoprolol: Increases serum concentration
- Nebivolol: Increases serum concentration
- Tizanidine: Increases serum concentration
- Tramadol: Diminishes therapeutic effect

Contraindications

Females who are or may become pregnant

Counseling Points

- Take on an empty stomach
- Do not crush or chew tablets; swallow whole with water
- Men who are sexually active with a pregnant woman must use a condom during and for 1 week after treatment with abiraterone acetate

Key Points

- Must be taken with at least oral prednisone 5 mg twice daily
- Food increases systemic exposure of abiraterone acetate by tenfold

Bicalutamide

Brand Name

Casodex

Generic Name

Bicalutamide

Rx Only

Dosage Forms

Tablet

Usage

Metastatic prostate cancer

Pregnancy Category X

Dosing

- Metastatic prostate cancer (in combination with a luteinizing hormone releasing hormone (LHRH) agonist): 50 mg once daily
- Hepatic dosage adjustment:
  - Moderate-to-severe impairment at treatment initiation: Use caution
  - Alanine aminotransferase >2 times the upper limit of normal or development of jaundice during treatment: Discontinue immediately

Adverse Reactions: Most Common

Hot flashes, back pain, weakness, diarrhea

Adverse Reactions: Rare/Severe/Important

Gynecomastia or breast pain (usually at higher, off-label dosing), interstitial lung disease (usually at higher doses), decreased bone mineral density, increased risk of cardiovascular disease, decreased libido

Major Drug Interactions

Bicalutamide's Effect on Other Drugs

Warfarin: Increases bleeding risk

Contraindications

Use in females, particularly females of childbearing age

Counseling Point

Take irrespective of meals, around the same time each day

Key Point

Bicalutamide should be given in combination with LHRH agonists

ANTIESTROGENS

Introduction

The available antiestrogens are selective estrogen receptor modulators (SERMs) commonly used for the treatment of breast cancer. Tamoxifen and raloxifene are also approved to prevent breast cancer in patients who are at high risk of the disease.

Mechanism of Action for the Drug Class

Compete with estrogen for binding sites in target tissues such as the breast, decreasing the effects of estrogen in those tissues.

Members of the Drug Class

In this section: Tamoxifen
Others: Toremifene, raloxifene

Tamoxifen

Brand Names

Nolvadex, Soltamox

Generic Name

Tamoxifen

Rx Only

Dosage Form

Tablet, oral solution

Usage

Breast cancer, *reduction in breast cancer incidence in high-risk women,* treatment of ductal carcinoma in situ

Pregnancy Category D

Dosing

- Treatment of metastatic breast cancer: 20–40 mg daily
- Adjuvant treatment for breast cancer, ductal carcinoma in situ, and reduction of breast cancer risk: 20 mg daily for 5 years

Adverse Reactions: Most Common

Hot flashes, mood changes, vaginal discharge or bleeding, menstrual irregularities, weight gain

Adverse Reactions: Rare/Severe/Important

Blood clots, hair loss, bone pain, endometrial hyperplasia, cataracts

Major Drug Interactions

Drugs Affecting Tamoxifen

- Strong inhibitors or inducers of CYP2C9, CYP2D6, and CYP3A4: Increase or decrease efficacy (may increase risk of breast cancer)
- SSRIs: Decrease effectiveness

Tamoxifen's Effect on Other Drugs

Warfarin: Increases anticoagulant effects

Contraindications

Women who require concomitant anticoagulant therapy, women with a history of deep vein thrombosis or pulmonary embolus (when tamoxifen is used for breast cancer risk reduction)

Counseling Points

- Take steps to avoid pregnancy when taking tamoxifen and during the 2 months after discontinuation
- Annual PAP smear and pelvic exam are recommended while on therapy
- Annual eye exams are recommended while on therapy

Key Points

- The benefits of tamoxifen as a treatment for breast cancer are firmly established and far outweigh the potential risks for most women
- Tamoxifen may help decrease bone loss in postmenopausal women

ANTIMETABOLITES

Introduction

This large class of antineoplastic drugs is similar in structure to naturally occurring compounds. All of the agents in this class cause GI side effects to varying degrees, depending on the agent, dose, and route of administration. Each agent also is associated with unique side effects.

Mechanism of Action for the Drug Class

Those compounds kill tumor cells by inhibiting DNA synthesis by a specific mechanism or they incorporate themselves into DNA, causing apoptosis. They generally have greater toxicity in rapidly growing cancer cells than normal cells of the host, but many of their toxicities arise from host cell effects.

Members of the Drug Class

In this section: Capecitabine, cytarabine, 5-fluorouracil, gemcitabine, mercaptopurine, methotrexate, pemetrexed
Others: Azacitidine, cladribine, clofarabine, decitabine, fludarabine, floxuridine, hydroxyurea, nelarabine, pralatrexate, pentostatin, thioguanine, trifluridine and tipiracil

◉ Capecitabine

Brand Name

Xeloda

Generic Name

Capecitabine

Rx Only

Dosage Form

Tablet

Usage

Metastatic colorectal cancer, adjuvant therapy of colon cancer, metastatic breast cancer, gastric cancer, pancreatic cancer, esophageal cancer, ovarian cancer, metastatic renal cell cancer, neuroendocrine tumors, metastatic CNS lesions

Pregnancy Category D

Dosing

- Individual protocols specify dosing for specific indications and institutions
- Usual dose: 1000–1250 mg/m^2 PO twice daily
- Renal dosage adjustment:
  - CrCl 30–50 ml/min: Administer 75% of dose
  - CrCl < 30 ml/min: Contraindicated
- Hepatic dosage adjustment: Avoid in severe impairment

Adverse Reactions: Most Common

Leukopenia, anemia, thrombocytopenia, nausea and vomiting, diarrhea, mucositis, skin discoloration, palmar-plantar erythrodysesthesia, eye irritation

Adverse Reactions: Rare/Severe/Important

Chest pain, venous thrombosis

Major Drug Interactions

Drugs Affecting Capecitabine

Leucovorin: Enhances toxic effect

Capecitabine's Effects on Other Drugs

Phenytoin: Increases serum concentration
Warfarin: Increases serum concentration

Contraindications

Known deficiency of dihydropyrimidine dehydrogenase (DPD), severe renal impairment (CrCl < 30 ml/min)

Counseling Points

- Report any fever, mouth sores, rashes, or diarrhea
- Avoid sunlight exposure and use sunscreen when exposure cannot be avoided
- Take with food
- Avoid use of antacids within 2 hours of taking medicine
- Do not crush, chew, or dissolve tablets

Key Points

- No live virus vaccines should be given during therapy
- Food reduces the rate and extent of absorption of capecitabine
- May cause a painful rash on the hands and feet

Cytarabine

Brand Name

ARA-C

Generic Name

Cytarabine

Rx Only

Dosage Form

Injection

Usage

Treatment of acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (blast phase), and lymphomas; prophylaxis and treatment of meningeal leukemia

Pregnancy Category D

Dosing

- Individual protocols specify dosing for specific indications and institutions
- Usual IV doses:
  - Children: 75–200 mg/m^2 for 5- to 10-day therapy
  - Adults:
    - 100–200 mg/m^2 daily for 5 to 10 days *or*
    - 100 mg/m^2 daily for 7 days *or*
    - 100 mg/m^2 per dose every 12 hours for 7 days *or*
    - High dose: 1–3 g/m^2 every 12 hours for up to 12 doses
- Usual intrathecal doses:
  - Adults: 5–75 mg/m^2 per dose every 2 to 7 days
  - Children:
    - 30 mg/m^2 per dose
    - Children < 3 years of age: Dose based on age
- Renal dosage adjustment:
  - No adjustment needed for 100–200 mg/m^2
  - High dose, CrCl 46–60 ml/min: Administer 60% of dose
  - High dose, CrCl 31–45 ml/min: Administer 50% of dose
  - High dose, CrCl < 30 ml/min: Avoid use
- Hepatic dosage adjustment: Reduce dose in severe dysfunction

Adverse Reactions: Most Common

Mucositis, diarrhea, nausea and vomiting, leucopenia, anemia, thrombocytopenia, conjunctivitis, alopecia

Adverse Reactions: Rare/Severe/Important

Chest pain, tumor lysis syndrome, neurotoxicity, coma, rash, skin desquamation, ocular toxicity

Counseling Points

- No live virus vaccines should be given during therapy
- Watch for fever, mouth sores, and diarrhea
- Stay well hydrated by drinking lots of fluids during therapy
- Report any changes in mental status
- May cause nausea and vomiting
- Increased risk of infection

Key Points

- Monitor for mental status changes during therapy
- Patients require aggressive hydration and antiemetic therapy
- May require prophylaxis for tumor lysis syndrome
- Myelosuppression can be severe and prolonged
- Patients require steroid eye drops to prevent ocular toxicities

5-Fluorouracil

Brand Names

5-FU, Adrucil, Carac, Efudex, Fluoroplex, Tolak

Generic Name

5-Fluorouracil

Rx Only

Dosage Forms
Injection, topical cream, topical solution

Usage
Treatment of carcinomas of the breast, colon, rectum, pancreas, stomach; head and neck cancer; anal cancer; cervical cancer; *topically for the management of actinic or solar keratoses and superficial basal cell carcinomas*

Pregnancy Category D

Dosing
- Individual protocols specify dosing for specific indications and institutions
- IV bolus:
  - 500–600 mg/m^2 per day weekly *or*
  - 425 mg/m^2 daily on days 1 to 5 every 4 weeks
- Continuous IV infusion:
  - 1,000 mg/m^2 daily for 4 to 5 days every 3 to 4 weeks *or*
  - 300–400 mg/m^2 daily *or*
  - 225 mg/m^2 daily for 5 to 8 weeks (with radiation therapy)
- Topical: Apply to lesions twice daily for 2 to 4 weeks
- Renal dosage adjustment: After dialysis, administer 50% of dose
- Hepatic dosage adjustment: If bilirubin ≥ 5 mg/dl, avoid use

Adverse Reactions: Most Common
Leukopenia, anemia, thrombocytopenia, nausea and vomiting, diarrhea, mucositis, skin discoloration, palmar-plantar erythrodysesthesia, eye irritation; skin irritation with topical formulation

Adverse Reactions: Rare/Severe/Important
Chest pain

Major Drug Interactions
Drugs Affecting 5-Fluorouracil
- Leucovorin: Increases both toxic effects and efficacy

5-Fluorouracil's Effect on Other Drugs
- Carvedilol: Increases serum concentrations
- Natalizumab: Increases toxicities
- Phenytoin: Increases serum concentration
- Warfarin: Increases bleeding risk

Counseling Points
- No live virus vaccines should be given during therapy
- Watch for fever, mouth sores, and diarrhea
- Avoid sunlight exposure and use sunscreen when exposure cannot be avoided
- Wash hands after using topical formulation
- Avoid drinking alcohol while taking this medication

Key Points
- Patients with a genetic deficiency of dihydropyrimidine dehydrogenase have increased systemic toxicities
- May be an irritant if it extravasates from the vein
- May cause severe diarrhea and mucositis

◉ Gemcitabine
Brand Name
Gemzar

Generic Name
Gemcitabine

Rx Only

Dosage Form
Injection

Usage
Metastatic breast cancer; locally advanced or metastatic non–small cell lung cancer (NSCLC) or pancreatic cancer; advanced, relapsed ovarian cancer, bladder cancer, cervical cancer, Hodgkin's disease, non-Hodgkin's lymphomas, *small cell lung cancer, hepatobiliary cancers*

Pregnancy Category D

Dosing
- Individual protocols specify dosing for specific indications and institutions
- 1000 mg/m^2 per day IV weekly up to 7 weeks followed by 1 week of rest
- Renal dosage adjustment: Caution with severe impairment; no specific recommendations on dose reductions are available

Adverse Reactions: Most Common
Leukopenia, thrombocytopenia, anemia, diarrhea, skin rash, nausea, flu-like symptoms, peripheral edema, proteinuria

Adverse Reactions: Rare/Severe/Important
Hematuria, hepatotoxicity

Major Drug Interactions
Gemcitabine's Effect on Other Drugs
- Bleomycin: Increases risk of pulmonary toxicity
- Fluorouracil: Increases serum concentration
- Warfarin: Increases bleeding risk

Counseling Points
- Watch for fever, bleeding, and bruising
- Flu-like symptoms can be severe; analgesics may be used to decrease those effects

Key Points

- No live virus vaccines should be given during therapy
- Rash is usually self-limiting
- Thrombocytopenia is common
- Flu-like symptoms may require the use of acetaminophen or NSAIDs
- Gemcitabine is a radiosensitizer and will increase the toxicity of radiation therapy, if used concurrently

Mercaptopurine

Brand Name

Purixan

Generic Name

Mercaptopurine

Rx Only

Dosage Form

Tablet, oral suspension

Usage

Treatment (maintenance and induction) of acute lymphoblastic leukemia (ALL); steroid-sparing agent for corticosteroid-dependent Crohn's disease (CD) and ulcerative colitis (UC); maintenance of remission in CD; fistulizing CD

Pregnancy Category D

Dosing

- Individual protocols specify dosing for specific indications and institutions
- Oncologic indications:
  - Induction: 2.5–5 mg/kg daily
  - Maintenance: 1.5–2.5 mg/kg daily or 80–100 mg/m^2 daily given once daily
- Reduction of steroid use in CD or UC, maintenance of remission in CD or fistulizing disease (unlabeled uses):
  - Initial: 50 mg PO daily
  - May increase by 25 mg daily every 1 to 2 weeks as tolerated to target dose of 1–1.5 mg/kg daily
- Renal dosage adjustment:
  - CrCl < 50 ml/min: Administer every 48 hours
  - Hemodialysis: Administer every 48 hours
- Hepatic dosage adjustment: Reduced dosage may be required

Adverse Reactions: Most Common

Leukopenia, thrombocytopenia, anemia, hepatotoxicity, drug fever, hyperpigmentation and rash

Adverse Reactions: Rare/Severe/Important

Encephalopathy, ascites

Major Drug Interactions

Drugs Affecting Mercaptopurine

- Allopurinol: Increases mercaptopurine levels
- Azathioprine: Increases mercaptopurine levels
- Febuxostat: Increases mercaptopurine levels

Mercaptopurine's Effect on Other Drugs

Warfarin: Effects may be inhibited

Counseling Points

- Watch for fever, malaise, bleeding, and bruising
- Take on an empty stomach

Key Points

- No live virus vaccines should be given during therapy
- Administration in the evening (vs morning administration) may lower the risk of relapse
- Dosage adjustment with concurrent allopurinol: Reduce mercaptopurine dosage by a quarter to a third of the usual dose
- TPMT genotyping may identify individuals at risk for toxicity
- Do not use the terms *6-mercaptopurine* or *6-MP* when writing prescriptions. The use of those terms has been associated with six-fold overdosage.

Methotrexate

Brand Name

Otrexup, Rasuvo, Trexall, Xatmep

Generic Name

Methotrexate

Rx Only

Dosage Forms

Injection, tablet, oral solution

Usage

- *Oncologic: Treatment of trophoblastic neoplasms (gestational choriocarcinoma, chorioadenoma destruens, and hydatidiform mole), acute lymphoblastic leukemia (ALL), meningeal leukemia,* breast cancer, head and neck cancer (epidermoid), cutaneous T-cell lymphoma (advanced mycosis fungoides), lung cancer (squamous cell and small cell), advanced non-Hodgkin's lymphomas, osteosarcoma
- Nononcologic: *Treatment of psoriasis (severe, recalcitrant, disabling) and severe rheumatoid arthritis (RA), including polyarticular-course juvenile rheumatoid arthritis (JRA); ectopic pregnancy;* Crohn's disease (CD)

Pregnancy Category X

Dosing

- Adult:
  - Individual protocols specify dosing for specific indications and institutions
  - Antineoplastic dosage range: Range is wide, from 30–40 mg/m^2 per week IV to 100–12,000 mg/m^2 with leucovorin rescue
  - RA: 7.5 mg PO once weekly or 2.5 mg PO every 12 hours for 3 doses per week, not to exceed 20 mg per week
  - Psoriasis:
    - 2.5–5 mg/dose PO every 12 hours for 3 doses given weekly *or*
    - 10–25 mg/dose PO or IM given once weekly
  - Ectopic pregnancy and abortion: 50 mg/m^2 IM once
  - Note that doses for oncologic indications are frequently much higher than for other uses
- Children:
  - JRA: 10 mg/m^2 PO or IM once weekly, then 5–15 mg/m^2 per week as a single dose or as 3 divided doses given 12 hours apart
  - Antineoplastic dosage range:
    - Oral, IM: 7.5–30 mg/m^2 per week or every 2 weeks
    - IV: Range: 10 mg/m^2 bolus dosing to 18,000 mg/m^2. Continuous infusion over 6 to 42 hours: Doses over 150 mg/m^2 will require leucovorin rescue.
    - Pediatric solid tumors:
      - < 12 years: 12 g/m^2 (dosage range: 12–18 g)
      - ≥ 12 years: 8 g/m^2 (maximum dose: 18 g)
    - Acute lymphoblastic leukemias
      - High-dose IV: Loading dose: 200 mg/m^2 followed by a 24-hour infusion of 1200 mg/m^2/day
      - Oral: Induction of remission in acute lymphoblastic leukemias: 3.3 mg/m^2/day for 4 to 6 weeks
      - Oral, IM: Remission maintenance: 20–30 mg/m^2 2 times/week
    - Meningeal leukemia: 6–12 mg/dose intrathecal based on age, up to a maximum of 12 mg/dose
- Renal dosage adjustment:
  - CrCl 61–80 ml/min: Administer 75% of dose
  - CrCl 51–60 ml/min: Administer 70% of dose
  - CrCl 10–50 ml/min: Administer 30–50% of dose
  - CrCl < 10 ml/min: Avoid use
  - Hemodialysis: Not dialyzable (0–5%); supplemental dose is not necessary
  - Peritoneal dialysis effects: Supplemental dose is not necessary
- Hepatic dosage adjustment: > 3 more than three times the upper limit of normal: Administer 75% dose
  - Bilirubin > 5 mg/dl: Do not administer

Adverse Reactions: Most Common

- Dependent on dose and route of administration
- Intrathecal 12 mg/m^2: Headache, myelosuppression, nausea
- Low oral dose (< 50 mg/week): Hepatotoxicity
- Moderate IV dose (50–100 mg/m^2): Leukopenia, nausea, vomiting, thrombocytopenia, anemia, diarrhea, mucositis
- High IV dose (>100 mg/m^2): Severe nausea and vomiting, alopecia, hepatotoxicity, renal toxicity, life-threatening myelosuppression, and mucositis (must give with leucovorin rescue)

Adverse Reactions: Rare/Severe/Important

Renal failure, arachnoiditis, encephalopathy (intrathecal administration), demyelinating encephalopathy, hepatotoxicity, sterility

Major Drug Interactions

Drugs Affecting Methotrexate

- Ciprofloxacin: May increase the serum concentration of methotrexate
- Cyclosporine: May increase the serum concentration of methotrexate
- NSAIDs: May reduce the excretion of methotrexate
- Penicillin: May decrease the excretion of methotrexate
- Proton pump inhibitors: May reduce the excretion of methotrexate
- Salicylates: Reduce methotrexate renal clearance and may displace methotrexate from binding sites
- Sulfonamides: Reduce methotrexate renal clearance and may displace methotrexate from binding sites

Methotrexate's Effect on Other Drugs

Cyclosporine: Levels may be increased

Contraindications

Pregnancy, breastfeeding, alcoholism, alcoholic liver disease, or other chronic liver disease

Counseling Points

- Watch for fever, malaise, bleeding, bruising, sore mouth and throat, and flank pain
- Avoid prolonged exposure to sunlight

Key Points

- No live virus vaccines should be given during therapy
- Cannot be administered with radiation therapy
- Use preservative-free solution when preparing methotrexate for intrathecal administration
- Doses between 1 mg/m^2 and 500 mg/m^2 may require leucovorin rescue, and doses > 500 mg/m^2 require leucovorin rescue:
  - IV, IM, Oral: Leucovorin 10–15 mg/m^2 every 6 hours for 8 or 10 doses, starting 24 hours after the start of methotrexate infusion. Continue until the methotrexate level is ≤ 0.1 micromolar (10^{-7} M)

- Leucovorin calcium must be given when using high doses of methotrexate to avoid severe life-threatening myelosuppression and mucositis
- Avoid use in patients with third spacing, such as ascites and effusions because of the reservoir effect
- Note that there is a wide spectrum of doses for methotrexate, depending on the indication. The antineoplastic doses are much higher than those for other inflammatory conditions, and logic should be used when the dose is assessed. Antineoplastic doses to a patient with rheumatoid arthritis can be fatal.

Pemetrexed

Brand Name
Alimta

Generic Name
Pemetrexed

Rx Only

Dosage Form
Injection

Usage
Mesothelioma, non–small cell lung cancer

Pregnancy Category D

Dosing
- IV: 500 mg/m^2 dose given once every 21 days
- Renal dosage adjustment: Use not recommended with a CrCl < 45 ml/min
- Hepatic dosage adjustment: If Grade 3 (5.1–20 times the upper limit of normal) *or* 4 (> 20 times upper limit of normal) transaminase elevation during treatment, then reduce pemetrexed dose to 75% of previous dose

Adverse Reactions: Most Common
Leukopenia, anemia, nausea, rash, stomatitis, fatigue, diarrhea

Adverse Reactions: Rare/Severe/Important
Interstitial pneumonia, severe cutaneous reactions, severe infections, hepatotoxicity

Major Drug Interactions
Drugs Affecting Pemetrexed

Ibuprofen: Increases concentration of pemetrexed

Pemetrexed's Effects on Other Drugs

Vaccines: Diminishes effect

Counseling Points
- Avoid use of NSAIDS several days before and after pemetrexed dosing
- Report any sign of infection, rash, or allergic reaction
- Take vitamin supplement as prescribed

Key Points
- Oral folic acid and injectable B_{12} must be given while on pemetrexed therapy to reduce risk of neutropenia
- Oral steroid therapy is required before and after pemetrexed to prevent rash

AROMATASE INHIBITORS

Introduction
Aromatase inhibitors are used in the adjuvant treatment of breast cancer as well as metastatic disease in postmenopausal women with hormone-positive tumors.

Mechanism of Action of the Drug Class
Those drugs competitively inhibit aromatase, an enzyme that converts androgens to estrogens. Some breast cancers are stimulated by estrogen and progesterone, and that reduces the available hormones in postmenopausal women.

Members of the Drug Class
In this section: Letrozole
Others: Anastrozole, exemestane

Letrozole

Brand Name
Femara

Generic Name
Letrozole

Rx Only

Dosage Form
Tablet

Usage
Adjuvant and metastatic treatment of breast cancer, ovarian cancer

Pregnancy Category X

Dosing

- Advanced breast cancer in postmenopausal women: 2.5 mg daily
- Adjuvant treatment for breast cancer in postmenopausal women: 2.5 mg daily for 5 years
- Ovarian cancer in postmenopausal women: 2.5 mg daily
- Hepatic dosage adjustment: In cases of severe hepatic dysfunction, reduce dose by 50% (2.5 mg every other day)

Adverse Reactions: Most Common

Musculoskeletal pain, nausea, hot flashes, headache, night sweats, weight gain, edema

Adverse Reactions: Rare/Severe/Important

Hypercholesterolemia, bone loss

Major Drug Interactions

Drugs Affecting Letrozole

Tamoxifen: May decrease the concentration of letrozole

Letrozole's Effects on Other Drugs

CYP2A6 substrates: Letrozole may increase the effects

Contraindications

Pregnancy

Counseling Points

- May cause nausea, hot flashes, musculoskeletal pain, and headache
- Can increase the risk of bone fractures and the development of osteoporosis

Key Points

- Aromatase inhibitors should only be used in postmenopausal women
- Aromatase inhibitors have been studied in the adjuvant treatment of breast cancer
- Aromatase inhibitors are well tolerated
- Bone loss is one of the most common concerns

IMMUNOMODULATORS

Introduction

Immunomodulators represent a class of agents used mainly for the management of multiple myeloma. Lenalidomide, for example, has become an important oral agent in the treatment of multiple myeloma.

Mechanism of Action for the Drug Class

The exact mechanism of the immunomodulators is unknown; however, those agents may be involved in anti-angiogenesis, direct suppression of tumor cell growth, tumor necrosis factor α, and other cytokines, immunomodulation through enhancement of natural killer (NK) and T-cell mediated cytotoxicity, or the promotion of hematopoietic stem cell differentiation.

Members of the Drug Class

In this section: Lenalidomide
Others: Pomalidomide, thalidomide

⦿ Lenalidomide

Brand Name

Revlimid

Generic Name

Lenalidomide

Rx Only

Dosage Form

Capsule

Usage

Myelodysplastic syndrome (MDS), *multiple myeloma,* mantle cell lymphoma

Pregnancy Category X

Dosing

- Mantle cell lymphoma, multiple myeloma: 25 mg PO once daily for 21 days of a 28-day treatment cycle
- Myelodysplastic syndrome (MDS) with deletion 5q: 10 mg PO once daily

Adverse Reactions: Most Common

Leukopenia, anemia, thrombocytopenia, thromboembolism, pruritus, rash

Adverse Reactions: Rare/Severe/Important

Severe skin rashes, including Stevens-Johnson syndrome; hepatotoxicity; secondary malignancies

Major Drug Interactions

Drugs Affecting Lenalidomide

- Dexamethasone: Increases thrombosis risk
- Immunosuppressants: Increase immunosuppressive effect

Lenalidomide's Effect on Other Drugs

- Vaccines: Diminished effect

Contraindication

Pregnancy

Counseling Points

- No live vaccines during therapy
- Report any fevers, bleeding, or bruising
- Report any sign of a clot, shortness of breath, or swelling in an extremity
- Woman of childbearing years must use birth control to avoid pregnancy
- Stop therapy if you become pregnant

Key Points

- May cause birth defects; do not use during pregnancy (contraindication). Patients must avoid pregnancy while taking lenalidomide.
- Women of childbearing potential: Pregnancy test 10 to14 days *and* 24 hours prior to initiating therapy, weekly during the first 4 weeks of treatment, then every 2 to 4 weeks through 4 weeks after therapy discontinued
- Distribution is restricted; physicians, pharmacists, and patients must be registered with the REVLIMID REMS® program
- Thrombosis prophylaxis is recommended if using with dexamethasone

MONOCLONAL ANTIBODIES

Introduction

Monoclonal antibodies comprise a group of targeted therapies that kill tumors by targeting oncogenes (i.e., genetic abnormalities of tumor cells) or specific surface antigens. All of them carry the risk of infusion reactions and skin rashes. Monoclonal antibodies are available for many other nononcologic diseases; only those used in the treatment of cancer are discussed here.

Mechanism of Action for the Drug Class

Those drugs are engineered antibodies that are human, murine, or chimeric combinations that target abnormal antigens and oncogenes on tumor cells. By binding to those receptors on tumor cells extracellularly, internal signaling pathways to grow and spread are inhibited, or "turned off," leading to cell death. Cetuximab and trastuzumab target epidermal growth factor receptors (EGFRs), whereas bevacizumab targets vascular endothelial growth factor (VEGF). Rituximab targets the antigen CD20 found on B-cell lymphocytes. Recently, monoclonal antibodies, known as immune checkpoint inhibitors, employ the immune system to achieve antitumor responses. Immune checkpoint inhibitors, like nivolumab, block the interaction between programmed cell death-1 (PD-1) and its ligands PD-L1 and PD-L2, allowing for antitumor immune responses via T-cell reactivation.

Members of the Drug Class

In this section: Bevacizumab, cetuximab, nivolumab, rituximab, trastuzumab

Others: Ado-trastuzumab, alemtuzumab, atezolizumab, avelumab, blinatumomab, daratumumab, durvalumab, elotuzumab, ipilimumab, necitumumab, ofatumumab, obinutuzumab, olaratumab, panitumumab, pembrolizumab, pertuzumab, ramucirumab, siltuximab

Bevacizumab

Brand Name

Avastin

Generic Name

Bevacizumab

Rx Only

Dosage Form

Injection

Usage

Metastatic colorectal cancer; nonsquamous, non-small cell lung cancer; metastatic renal cell carcinoma; malignant glioblastoma; metastatic, persistent, recurrent cervical cancer; platinum-resistant recurrent ovarian (epithelial), fallopian tube, or primary peritoneal cancer

Pregnancy Category C

Dosing

- 5 or 10 mg/kg IV every 2 weeks *or*
- 15 mg/kg IV every 3 weeks

Adverse Reactions: Most Common

Hypertension, proteinuria, rash, hypersensitivity reactions

Adverse Reactions: Rare/Severe/Important

Arterial thrombosis, bleeding, poor wound healing, nephrotic syndrome, bowel perforation, reversible leukoencephalopathy

Major Drug Interactions

Drugs Affecting Bevacizumab

- Sunitinib: May increase toxicity

Bevacizumab's Effects on Other Drugs

- Irinotecan: Increases toxicity
- Sunitinib: Increases hypertensive effects
- Sorafenib: Increases toxicity
- Anthracyclines: Increases cardiotoxicity

Contraindications

Use within 4 weeks of surgery, uncontrolled hypertension

Counseling Points

- Report any signs of bleeding or thrombosis
- Hypersensitivity reactions and rash may occur

Key Points

- Monitor blood pressure with treatment visits, and treat hypertension, if needed
- Monitor for proteinuria
- Monitor for signs of bleeding

◉ Cetuximab

Brand Name

Erbitux

Generic Name

Cetuximab

Rx Only

Dosage Form

Injection

Usage

Metastatic K-RAS negative colorectal cancer, squamous cell head and neck cancer, EGFR+ non–small cell lung cancer

Pregnancy Category C

Dosing

- Initial loading dose: 400 mg/m^2 IV
- Maintenance dose: 250 mg/m^2 IV weekly

Adverse Reactions: Most Common

Hypersensitivity, acneiform rash, diarrhea, hypomagnesemia

Adverse Reactions: Rare/Severe/Important

Sepsis, severe infusion reactions

Counseling Points

- Report any rashes
- Acne rash is an expected reaction. It may require treatment with topical or oral antibiotics.
- Avoid direct sunlight for 2 months after therapy is completed

Key Points

- Magnesium, potassium, and calcium levels should be monitored
- Acneiform rash may require treatment with antibiotics, if severe
- Premedication with corticosteroid and diphenhydramine is recommended to prevent hypersensitivity reactions

◉ Nivolumab

Brand Name

Opdivo

Generic Name

Nivolumab

Rx Only

Dosage Forms

Injection

Usage

Metastatic, progressive non–small cell lung cancer, metastatic melanoma, advanced renal cell carcinoma who received prior antiangiogenic therapy, recurrent or metastatic squamous cell carcinoma of the head and neck, locally advanced or metastatic urothelial carcinoma, relapsed or progressive classical Hodgkin's lymphoma after auto-hematopoietic stem cell transplant (HSCT) and post-HSCT brentuximab

Pregnancy Category

Not assigned, but fetal harm is considered likely

Dosing

- Unresectable or metastatic melanoma, metastatic, progressive lung cancer, advanced renal cell carcinoma, locally advanced or metastatic urothelial carcinoma: 240 mg every 2 weeks
- Unresectable metastatic melanoma with concurrent ipilimumab: nivolumab 1 mg/kg, followed by ipilimumab on the same day, every 3 weeks for 4 doses, then nivolumab 240 mg every 2 weeks

- Classical Hodgkin's lymphoma, recurrent or metastatic squamous cell carcinoma of the head and neck: 3 mg/kg every 2 weeks
- Renal dosage adjustment: Only required if renal toxicity during treatment
- Hepatic dosage adjustment: Only required if hepatotoxicity during treatment

Adverse Reactions: Most Common

Rash, fatigue, musculoskeletal pain, pruritus, nausea, cough, dyspnea, constipation or diarrhea, back pain, arthralgia, decreased appetite

Adverse Reactions: Rare/Severe/Important

Immune-mediated toxicities, including pneumonitis, colitis, hepatitis, endocrinopathies (hypophysitis, adrenal insufficiency, pancreatitis, hyperthyroidism, hypothyroidism), nephritis, renal dysfunction, skin reactions, encephalitis

Major Drug Interactions

Drugs affecting Nivolumab

Immunosuppressants: Diminishes therapeutic effect

Counseling Points

- Women of childbearing age should use effective contraception during and for at least 5 months following the last dose of nivolumab
- Report any signs of immune-mediated toxicities, including new or worsening cough; chest pain; shortness of breath; loose, dark, and/or dark stools; abdominal pain; bleeding or bruising more easily; severe nausea or vomiting, headaches; weight gain or weight loss; rash; swelling of lower extremities; fever; confusion; seizures; corticosteroids may be required to manage the majority of the immune-mediated side effects

Key Point

Dosing varies, depending on the indication and if nivolumab is given concurrently with ipilimumab

Rituximab

Brand Name

Rituxan

Generic Name

Rituximab

Rx Only

Dosage Form

Injection

Usage

B-cell non-Hodgkin's lymphoma, chronic lymphocytic leukemia (CLL), rheumatoid arthritis (RA), Burkitt's lymphoma, CNS lymphoma, Hodgkin's lymphoma (lymphocyte predominant); MALT lymphoma (gastric and nongastric), splenic marginal zone lymphoma, small lymphocytic lymphoma (SLL), Waldenström's macroglobulinemia, autoimmune hemolytic anemia in children, chronic idiopathic thrombocytopenic purpura, refractory pemphigus vulgaris, systemic autoimmune diseases (other than RA), steroid-refractory chronic graft-versus-host disease

Pregnancy Category C

Dosing

- Usual dosing: 375 mg/m^2 IV weekly
- RA: 1000 mg on days 1 and 15 in combination with methotrexate
- Infusion notes:
  - Initial infusion: Start rate of 50 mg/hour; if there is no reaction, increase the rate 50 mg/hour every 30 minutes, to a maximum of 400 mg/hour
  - Subsequent infusions: If patient did not tolerate initial infusion well, follow initial infusion guidelines. If patient tolerated initial infusion, start at 100 mg/hour; if there is no reaction, increase the rate by 100 mg/hour every 30 minutes, to a maximum of 400 mg/hour.
  - If a reaction occurs, slow or stop the infusion. If the reaction abates, restart the infusion at 50% of the previous rate.

Adverse Reactions: Most Common

Infusion reaction, tumor lysis syndrome, lymphopenia, rash, nausea, myalgias, arthralgias

Adverse Reactions: Rare/Severe/Important

Severe and sometimes fatal mucocutaneous reactions (lichenoid dermatitis, paraneoplastic pemphigus, Stevens-Johnson syndrome, toxic epidermal necrolysis, and vesiculobullous dermatitis); anaphylaxis; progressive multifocal leukoencephalopathy; bowel obstruction and perforation

Major Drug Interactions

Rituximab's Effect on Other Drugs

Antihypertensives: Hypotension may be increased

Counseling Points

- Immediately report any shortness of breath, chest tightness, fever, or chills during treatments
- The risk of infection is increased while on treatment

Key Points

- No live virus vaccines during therapy
- Infusion-related reactions are common. Monitor the patient during the infusion.
- Pretreatment with acetaminophen and diphenhydramine is recommended
- Reactivation of hepatitis B and other serious viral infections (possibly new or reactivated) have been reported

◉ Trastuzumab

Brand Name
Herceptin

Generic Name
Trastuzumab

Rx Only

Dosage Form
Injection

Usage
Early stage and metastatic breast cancer

Pregnancy Category D

Dosing
IV 4 mg/kg loading dose, then 2 mg/kg weekly or 6 mg/kg every 3 weeks

Adverse Reactions: Most Common
Infusion-related reactions, rash, nausea, diarrhea

Adverse Reactions: Rare/Severe/Important
Cardiotoxicity, pulmonary toxicity

Major Drug Interactions

Trastuzumab's Effect on Other Drugs

- Anthracyclines: Increase cardiotoxicity
- Myelosuppressive chemotherapy: Increases infection risk

Counseling Point
Immediately report any shortness of breath, chest tightness, fever, or chills during treatments

Key Point
Patients should have ejection fraction measured before starting therapy

PLATINUM COMPOUNDS

Introduction
Similar to alkylating agents, platinum compounds are cell cycle–nonspecific agents that are directly toxic to DNA by causing strand breaks to form. They are used in the treatment of a variety of malignant diseases. All of them cause some degree of neurotoxicity but also possess unique toxicities.

Mechanism of Action for the Drug Class
Form strong covalent bonds with DNA, inhibiting replication and causing cell death

Members of the Drug Class
Carboplatin, cisplatin, oxaliplatin

◉ Carboplatin

Brand Name
Paraplatin-AQ

Generic Name
Carboplatin

Rx Only

Dosage Form
Injection

Usage
Treatment of ovarian cancer, lung cancer, head and neck cancer, endometrial cancer, esophageal cancer, *bladder cancer,* breast cancer, cervical cancer, CNS tumors, germ cell tumors, osteogenic sarcoma, and high-dose therapy with stem cell/bone marrow support

Pregnancy Category D

Dosing

- Individual protocols specify dosing for specific indications and institutions
- Children:
  - Solid tumor: 300–600 mg/m^2 once every 4 weeks
  - Brain tumor: 175 mg/m^2 weekly for 4 weeks every 6 weeks, with a 2-week recovery period between courses
- Adults:
  - 300–360 mg/m^2 IV every 3 to 4 weeks or target area under the curve (AUC) of 5–7 mg given every 3 weeks dosed by the Calvert equation
    - Calvert equation: Dose = AUC (glomerular filtration rate [GFR] + 25)
  - Autologous bone marrow transplant: 1600 mg/m^2 (total dose) IV divided over 4 days
- Renal dosage adjustment:
  - Renal dosing based on the Calvert equation: Dose = AUC (GFR + 25)
  - CrCl 41–59 ml/min: Initiate at 250 mg/m^2
  - CrCl 16–40 ml/min: initiate at 200 mg/m^2

Adverse Reactions: Most Common

Leuopenia, anemia, thrombocytopenia, nausea and vomiting, peripheral neuropathies, alopecia

Adverse Reactions: Rare/Severe/Important

Ototoxicity, hypersensitivity

Major Drug Interactions

Drugs Affecting Carboplatin

Aminoglycosides: Increase risk of ototoxicity

Carboplatin's Effect on Other Drugs

Taxanes: Increase bone marrow suppression

Contraindications

Severe allergic reaction to carboplatin, cisplatin, other platinum-containing formulations, mannitol, or any component of the formulation; should not be used in patients with severe bone marrow depression or significant bleeding

Counseling Points

- This drug may cause severe fetal defects; avoid pregnancy and breastfeeding during therapy
- Drink plenty of fluids after chemotherapy
- Severe nausea and vomiting could occur for several days after chemotherapy
- Contact your healthcare provider if you are unable to keep food or fluids down
- Contact your healthcare provider if there is any hearing loss

Key Points

- No live virus vaccines during therapy
- May be an irritant if it extravasates from the vein
- Hypersensitivity risk increases with more than six treatments

◉ Cisplatin

Brand Names

Platinol, Platinol-AQ

Generic Names

Cisplatin, CDDP

Rx Only

Dosage Form

Injection

Usage

Bladder cancer, testicular cancer, ovarian cancer, head and neck cancer, breast cancer, gastric cancer, esophageal cancer, cervical cancer, prostate cancer, *non–small cell lung carcinoma (NSCLC), small cell lung cancer,* Hodgkin's and non-Hodgkin's lymphoma, neuroblastoma, sarcoma, myeloma, melanoma, mesothelioma, osteosarcoma

Pregnancy Category D

Dosing

- Individual protocols specify dosing for specific indications and institutions
- Children:
  - 37–100 mg/m^2 every 21 to 28 days *or*
  - 15–20 mg/m^2 daily for 5 days every 3 to 4 weeks
- Adults:
  - 10–20 mg/m^2 daily for 5 days every 3 to 4 weeks *or*
  - 50–120 mg/m^2 every 3 to 4 weeks
  - Maximum dose: 120 mg/m^2 per cycle
  - High-dose bone marrow transplant: 55 mg/m^2 daily for 3 days, 165 mg/m^2 total
- Renal dosage adjustment:
  - CrCl 46–60 ml/min: Administer 75% of dose
  - CrCl 31–45 ml/min: Administer 50% of dose
  - CrCl < 30 ml/min: Consider use of alternative drug
  - Hemodialysis: Administer 50% of normal dose postdialysis

Adverse Reactions: Most Common

Nausea and vomiting, peripheral neuropathies, anemia, alopecia, nephrotoxicity, electrolyte imbalances

Adverse Reactions: Rare/Severe/Important

Ototoxicity

Major Drug Interactions

Drugs Affecting Cisplatin

- Aminoglycosides: Increase nephrotoxicity
- Amifostine: Can reduce nephrotoxicity
- Taxanes: Increase bone marrow suppression

Cisplatin's Effect on Other Drugs

- Topotecan: Reduces clearance
- Vinorelbine: Increases risk of neutropenia

Contraindications

Hypersensitivity to cisplatin, other platinum-containing compounds, or any component of the formulation (anaphylactic-like reactions have been reported); preexisting renal impairment; myelosuppression; hearing impairment

Counseling Points

- This drug may cause severe fetal defects; avoid pregnancy and breastfeeding during therapy
- Drink plenty of fluids after chemotherapy
- Severe nausea and vomiting could occur for several days after chemotherapy
- Contact your healthcare provider if unable to keep food or fluids down
- Contact healthcare provider if there is any hearing loss

Key Points

- Verify any dose > 100 mg/m²
- Assess renal function prior to administration
- Assess electrolytes, particularly potassium and magnesium, and replace as needed
- IV hydration should be given before and after cisplatin therapy
- Mannitol or furosemide can be given to reduce nephrotoxicity
- Highly emetogenic; premedicate to prevent nausea and vomiting
- Patients should also receive antiemetics after chemotherapy to prevent delayed emesis
- Ototoxicity is more pronounced in children

◉ Oxaliplatin

Brand Name

Eloxatin

Generic Name

Oxaliplatin

Rx Only

Dosage Form

Injection

Usage

Colorectal cancer, head and neck cancers, gastric cancer, pancreatic cancer

Pregnancy Category D

Dosing

- Individual protocols specify dosing for specific indications and institutions
- Typically dosed 85 mg/m² IV every 2 weeks with 5-fluorouracil regimens
- Renal dosage adjustment: If CrCl <30 ml/min, reduce dose from 85 mg/m² to 65 mg/m²

Adverse Reactions: Most Common

Leuopenia, anemia, thrombocytopenia, nausea and vomiting, peripheral neuropathies, thermal dysesthesias, alopecia

Adverse Reactions: Rare/Severe/Important

Hypersensitivity reactions, peripheral neuropathies, pulmonary fibrosis, hepatotoxicity, reversible posterior leukoencephalopathy

Major Drug Interactions

Oxaliplatin's Effects on Other Drugs

- Taxanes: Increase bone marrow suppression
- Vaccines: May have diminished effect

Contraindications

Severe allergic reaction to carboplatin, cisplatin, other platinum-containing formulations, mannitol, or any component of the formulation; should not be used in patients with severe bone marrow depression or significant bleeding

Counseling Points

- Allergic reaction can occur during the infusion
- Report any sign of infection, bleeding, or bruising
- Report any numbness or tingling in hands and feet
- Do not eat or drink anything cold 3 to 4 days after chemotherapy; everything must be warm or room temperature
- Wear gloves in cold weather
- Breathing cold air may cause throat pain

Key Points

- Monitor for hypersensitivity reactions during infusion
- No live virus vaccines during therapy
- Because it is a vesicant, it can cause tissue damage if it extravasates from the vein

PROTEASOME INHIBITORS

Introduction

Proteasome inhibitors represent a newer class of agents that degrade intracellular proteins, enzymes, and transcription factors, which inhibits cell cycle progression and induces apoptosis. Proteasome inhibitors are primarily used for the management of multiple myeloma and other select hematologic malignancies.

Mechanism of Action for the Drug Class

Bortezomib, the first proteasome inhibitor to be approved, blocks proteasomes, or enzyme complexes responsible for regulating protein homeostasis within the cell.

Members of the Drug Class

In this section: Bortezomib
Others: carfilzomib, ixazomib

Bortezomib

Brand Name
Velcade

Generic Name
Bortezomib

Rx Only

Dosage Form
Injection

Usage
Multiple myeloma, mantle cell lymphoma

Pregnancy Category D

Dosing
- Individual protocols specify dosing for specific indications and institutions
- Multiple myeloma
  - IV, SUB-Q: 1.3 mg/m^2 days 1, 4, 8, 11, 22, 25, 29, and 32 of a 42-day treatment cycle
- Mantle cell lymphoma
  - IV, SUB-Q: 1.3 mg/m^2 days 1, 4, 8, 11 of a 21-day treatment cycle

Adverse Reactions: Most Common
Leukopenia, anemia, thrombocytopenia, nausea, herpes reactivation, peripheral neuropathies, hypotension, diarrhea

Adverse Reactions: Rare/Severe/Important
Hepatotoxicity, reversible posterior leukoencephalopathy, tumor lysis syndrome, pneumonitis

Major Drug Interactions
Drugs Affecting Bortezomib
- Ascorbic acid: May diminish therapeutic effect
- Moderate CYP2C19 inhibitors: May decrease metabolism
- Strong CYP3A4 inducers: May increase metabolism
- Moderate CYP3A4 inhibitors: May decrease metabolism
- Grapefruit juice: May increase levels
- Green tea: May reduce effect
- St John's Wort: May decrease serum concentration

Bortezomib's Effect on Other Drugs
- Clopidogrel: Decreases serum concentrations of the active metabolite(s) and decreases effect

Contraindications
Allergy to boron or mannitol; administration via the intrathecal route

Counseling Points
- Report any signs of infection, bleeding, or bruising
- Numbness and tingling in hands and feet can occur with continued therapy
- Avoid use of ascorbic acid, green tea, and grapefruit juice on treatment days
- No live virus vaccines during therapy

Key Points
- Consider prophylaxis of herpes simplex infections with antivirals
- Peripheral neuropathies can be severe
- Caution with using SSRIs while on therapy
- Not for intrathecal use; fatalities reported

TAXANES

Introduction
This class of antineoplastics is used to treat a wide range of malignancies. Taxanes can be used alone as monotherapy or in combination with other antineoplastics. From a toxicity standpoint, they are most notable for causing bone marrow suppression and peripheral neuropathies.

Mechanism of Action for the Drug Class
Taxanes stabilize the microtubule bundles by promoting assembly and preventing depolymerization, thereby inhibiting cell replication

Members of the Drug Class
In this section: Docetaxel, paclitaxel
Others: Cabazitaxel, protein-bound paclitaxel

Docetaxel

Brand Name
Taxotere

Generic Name
Docetaxel

Rx Only

Dosage Form
Injection

Usage
Breast cancer, locally advanced or metastatic non–small cell lung cancer, hormone-refractory metastatic prostate cancer, advanced gastric adenocarcinoma, locally advanced squamous cell head and neck cancer, bladder cancer, ovarian cancer, small cell lung cancer, soft tissue sarcoma

Pregnancy Category D

Dosing
- Individual protocols specify dosing for specific indications and institutions
- Dosage range: 60–100 mg/m^2/dose every 3 to 4 weeks *or* 35 mg/m^2 weekly
- Hepatic dosage adjustment: Avoid if either of the following are present:
  - Total bilirubin greater than the upper limit of normal
  - Aspartate aminotransferase/alanine aminotransferase > 1.5 times the upper limit of normal concomitant with alkaline phosphatase > 2.5 times the upper limit of normal

Adverse Reactions: Most Common
Fluid retention syndrome, leukopenia, anemia, thrombocytopenia, alopecia, peripheral neuropathies, myalgias, arthralgias, diarrhea, stomatitis, mild nausea

Adverse Reactions: Rare/Severe/Important
Skin desquamation, hypersensitivity, oncolysis

Major Drug Interactions
Drugs Affecting Docetaxel
- Azole antifungals: Decrease metabolism of docetaxel, raising concentrations
- Carboplatin, cisplatin: Increase myelosuppression

Contraindications
Severe hypersensitivity to other medications containing polysorbate 80; neutrophil count < 1500/mm^3

Counseling Points
- No live virus vaccines during therapy
- Watch for fever, malaise
- Risk of infection is increased; report any fever or infection

Key Points
- Extravasation can cause tissue necrosis
- Must premedicate with a corticosteroid to reduce fluid retention
- Administer taxane derivatives before platinum derivative when given as sequential infusions to limit toxicity

◉ Paclitaxel

Brand Name
Taxol

Generic Name
Paclitaxel

Rx Only

Dosage Form
Injection

Usage
Breast cancer, non–small cell lung cancer, locally advanced squamous cell head and neck cancer, bladder cancer, *ovarian cancer,* small cell lung cancer, adenocarcinomas of unknown primary, and AIDS-related Kaposi's sarcoma

Pregnancy Category D

Dosing
- Individual protocols specify dosing for specific indications and institutions
- Dosage range: 135–200 mg/m^2 per dose every 3 to 4 weeks *or* 80–100 mg/m^2 weekly
- Hepatic dosage adjustment: (3-hour infusion):
  - Transaminase levels < 10 times the upper limit of normal and bilirubin level 1.26 to 2 times the upper limit of normal: 135 mg/m^2
  - Transaminase levels < 10 times the upper limit of normal and bilirubin level 2.01 to 5 times the upper limit of normal: 90 mg/m^2
  - Transaminase levels ≥ 10 times the upper limit of normal and bilirubin level > 5 times the upper limit of normal: Avoid use

Adverse Reactions: Most Common
Bradycardia, flushing, leukopenia, anemia, thrombocytopenia, alopecia, peripheral neuropathies, myalgias, arthralgias, diarrhea, stomatitis, mild nausea

Adverse Reactions: Rare/Severe/Important
Hypersensitivity, skin rashes

Major Drug Interactions
Drugs Affecting Paclitaxel
- Azole antifungals: Decrease the metabolism of paclitaxel, increasing concentrations
- Carboplatin, cisplatin: Increase myelosuppression
- Trastuzumab: Enhances neutropenia

Paclitaxel's Effect on Other Drugs
- Anthracyclines: Increase cardiotoxicity

Contraindications
Hypersensitivity to paclitaxel, Cremophor EL (polyoxyethylated castor oil), or any component of the formulation, treatment of solid tumors in patients with baseline neutrophil

counts < 1500/mm^3; treatment of Kaposi's sarcoma in patients with baseline neutrophil counts < 1000/mm^3

Counseling Points

- No live virus vaccines during therapy
- Peripheral neuropathies can occur with continued use
- Risk of infection is increased; report any fever or infection

Key Points

- Severe bone marrow suppression is possible and may require dose reduction
- Monitor blood pressure regularly while drug is infusing
- Extravasation can cause tissue necrosis
- Must premedicate with a corticosteroid, diphenhydramine, and histamine-2 blocker to prevent hypersensitivity
- Paclitaxel is a radiosensitizer and will increase the effect and toxicity of radiation therapy
- Administer a taxane derivative before a platinum derivative when given as sequential infusions to limit toxicity

TOPOISOMERASE INHIBITORS

Introduction

Members of this class of antineoplastics, also known as podophyllotoxins, are extracted from the mandrake plant, with recorded use dating back to colonial America as a cathartic agent. Today, etoposide is the most commonly used agent in the class and has important utility in the treatment of a variety of cancers.

Mechanism of Action for the Drug Class

Antineoplastics in this class are cell cycle–specific and arrest cell division in the premitotic phase by inhibiting topoisomerase enzymes that are required for normal DNA repair. Etoposide inhibits TOPO-II enzymes, whereas topotecan and irinotecan inhibit TOPO I enzymes. Both topotecan and irinotecan are frequently used agents for multiple solid tumors, such as ovarian, lung, and colorectal cancers.

Members of the Drug Class

In this section: Etoposide, irinotecan, topotecan
Others: Teniposide

◉ Etoposide

Brand Name

Toposar

Generic Name

Etoposide

Rx Only

Dosage Forms

Capsule, injection

Usage

Ovarian cancer (oral), small cell lung cancer, testicular cancer

Pregnancy Category D

Dosing

- Individual protocols specify dosing for specific indications and institutions
- Oral: 30–50 mg/m^2 on days 1 to 21 every 28 days
- IV:
  - 80–120 mg/m^2 on days 1 to 3 every 21 days *or*
  - 100 mg/m^2 on days 1 to 5 every 21 days
- Nonseminoma, metastatic (high-dose regimens): 750 mg/m^2 per day IV administered 5, 4, and 3 days before peripheral blood stem cell infusion
- Renal dosage adjustment:
  - CrCl 15–50 ml/min: Administer 75% of dose
  - CrCl < 15 ml/min: Data not available; consider further dose reductions

Adverse Reactions: Most Common

Leukopenia, anemia, thrombocytopenia, alopecia, nausea, vomiting

Adverse Reactions: Rare/Severe/Important

Severe skin reactions, hypotension, extravasation. Note that the following may occur with higher doses used in stem cell transplantation: Alopecia; ethanol intoxication; hepatitis; hypotension (infusion related); metabolic acidosis, mucositis, nausea, and vomiting (severe); secondary malignancy; and skin lesions (resembling Stevens-Johnson syndrome).

Major Drug Interactions

Drugs Affecting Etoposide

- Atovaquone: May increase levels
- CYP3A4 inducers or major substrates: May diminish effect
- CYP3A4 inhibitors: May increase effect or toxicity
- Phenytoin: May decrease blood levels
- St. John's wort: May decrease levels

Etoposide's Effect on Other Drugs

- Other substrates of CYP3A4: May decrease effect
- Vaccines: May have a diminished effect
- Warfarin: Effects may be enhanced

Counseling Points

- Watch for fever, malaise, sore mouth or throat, pain or swelling at injection site
- No live virus vaccines during therapy
- Risk of infection is increased; report any fever or infection
- Oral etoposide should be stored in the refrigerator at 2°C to 8°C (36°F to 46°F)

Key Points

- IV administration commonly given in a regimen with additional chemotherapy agents
- Oral etoposide has poor bioavailability but is used as single agent in advanced ovarian cancer
- Leukopenia and alopecia are the most common adverse effects seen with typical dosing. High doses used pre-stem cell transplant have more significant adverse effects.

◉ Irinotecan

Brand Name

Camptosar

Generic Name

Irinotecan

Rx Only

Dosage Form

Injection

Usage

Metastatic colorectal cancer, non–small cell lung cancer, ovarian cancer, gastric cancer, small cell lung cancer, pancreatic cancer, central nervous system cancer, cervical cancer

Pregnancy Category D

Dosing

- Individual protocols specify dosing for specific indications and institutions
- Metastatic colorectal cancer:
  - 125 mg/m² weekly for 4 weeks on and 2 weeks off of a 6-week cycle *or*
  - 350 mg/m² IV once every 3 weeks
- Hepatic dosage adjustment:
  - Bilirubin > the upper limit of normal to ≤ 2 mg/dl: Consider reducing initial dose by one dose level
  - Bilirubin > 2 mg/dl: Use is not recommended

Adverse Reactions: Most Common

Leukopenia, anemia, thrombocytopenia, diarrhea, cramping, nausea, vomiting, dehydration

Adverse Reactions: Rare/Severe/Important

Dehydration, diarrhea, colitis, intestinal perforation

Major Drug Interactions

Drugs Affecting Irinotecan

- Bevacizumab: May enhance the adverse/toxic effects
- Carbamazepine: May decrease serum concentrations
- CYP3A4 inducers or major substrates: May diminish effect
- CYP3A4 inhibitors: May increase effects or toxicity
- Phenytoin: May decrease blood levels
- St. John's wort: May decrease levels

Irinotecan's Effect on Other Drugs

- Other substrates of CYP3A4: May decrease effects
- Vaccines: May have a diminished effect
- Warfarin: Effects may be enhanced

Counseling Points

- No live virus vaccines during therapy
- Loperamide should be used at the first sign of diarrhea
- Report any signs of infection, bleeding, or bruising
- Report any diarrhea or cramping and vomiting

Key Points

- Patients should be given loperamide as needed for delayed diarrhea
- Acute diarrhea and cramping during the infusion is a cholinergic reaction and should be treated with atropine

◉ Topotecan

Brand Name

Hycamtin

Generic Name

Topotecan

Rx Only

Dosage Forms

Capsule, injection

Usage

Ovarian cancer, small cell lung cancer, cervical cancer

Pregnancy Category D

Dosing

- Individual protocols specify dosing for specific indications and institutions
- IV: 1.5 mg/m^2 per day for 5 days every 21 days
- Oral: 2.3 mg/m^2 daily for 5 days every 21 days
- Renal dosage adjustment:
  - CrCl 20–39 ml/min: Reduce dose to 0.75 mg/m^2
  - CrCl < 20 ml/min: Insufficient data available for dosing recommendation

Adverse Reactions: Most Common

Leukopenia, anemia, thrombocytopenia, diarrhea

Adverse Reactions: Rare/Severe/Important

Interstitial lung disease, neutropenic colitis, neutropenic fevers

Major Drug Interactions

Drugs Affecting Topotecan

- Cisplatin: May increase toxicity
- Clozapine: May increase the risk of agranulocytosis

Topotecan's Effect on Other Drugs

- Vaccines: May have a diminished effect

Contraindications

Neutropenia

Counseling Points

- No live virus vaccines during therapy
- Report any signs of infection, bleeding, or bruising
- Risk of infection is increased; report any fevers
- Report any unresolved diarrhea, nausea, or vomiting
- Capsules must be swallowed whole with or without food

Key Points

- Use of prophylactic G-CSF can reduce the incidence of neutropenic fevers
- Do not administer chemotherapy if neutrophil count < 1500/mm^3 or platelets < 100,000/mm^3

TYROSINE KINASE INHIBITORS

Introduction

Tyrosine kinase inhibitors are a large class of oral targeted agents available to treat various malignancies. Each inhibits the protein tyrosine kinase and has an effect on specific growth factor receptors that stimulate tumor growth.

Mechanism of Action for the Drug Class

Tyrosine kinase inhibitors specifically target genetic abnormalities in cancers that push the cell to divide, grow, and spread. Those agents inhibit the oncogene proteins intracellularly, blocking the signaling pathway and ultimately slowing or stopping tumor cell proliferation. Erlotinib targets the tyrosine kinase of EGFR (epidermal growth factor receptor), whereas imatinib targets the Breakpoint Cluster Region-Abelson (BCR-ABL) fusion gene of the Philadelphia chromosome. Ibrutinib is a newer tyrosine kinase inhibitor that specifically targets Bruton's tyrosine kinase (BTK), an essential component of the B-cell receptor and cytokine receptor pathway. Inhibition of BTK ultimately results in decreased malignant B-cell proliferation and survival.

Members of the Drug Class

In this section: Erlotinib, ibrutinib, imatinib
Others: Afatinib, alectinib, axitinib, brigatinib, bosutinib, cabozantinib, ceritinib, crizotinib, dasatinib, gefitinib, lapatinib, lenvatinib, midostaurin, nilotinib, osimertinib, pazopinib, ponatinib, regorafenib, ruxolitinib, sorafenib, sunitinib, vandetanib

◉ Erlotinib

Brand Name

Tarceva

Generic Name

Erlotinib

Rx Only

Dosage Form

Tablet

Usage

Non–small cell lung cancer, pancreatic cancer

Pregnancy Category D

Dosing

- 100 mg or 150 mg oral daily
- Smokers: A dose increase to a maximum of 300 mg (with careful monitoring) may be required in patients who continue to smoke
- Hepatic dosage adjustment: If total bilirubin > 3 times the upper limit of normal, use extreme caution

Adverse Reactions: Most Common

Diarrhea, nausea, edema, acneiform rash

Adverse Reactions: Rare/Severe/Important

Severe skin reactions, GI perforation, interstitial pneumonitis, hepatotoxicity

Major Drug Interactions

Drugs Affecting Erlotinib

- Antacids: May decrease absorption
- CYP3A4 inhibitors: May increase toxicity
- CYP3A4 inducers: May decrease efficacy
- Grapefruit: May increase serum concentration
- Proton pump inhibitors: May reduce serum concentrations

Erlotinib's Effect on Other Drugs

- Warfarin: Effects may be enhanced

Counseling Points

- Take on an empty stomach
- Avoid grapefruit or grapefruit juice around dosing time
- Maintain adequate hydration
- Report any rashes, swelling, or respiratory symptoms
- Notify healthcare provider right away if smoking status changes

Key Points

- Food will increase bioavailability
- Verify smoking status; smokers require higher dosing
- Dose adjustments needed if used with CYP3A4 inhibitors or inducers or major substrates

⦿ Ibrutinib

Brand Name

Imbruvica

Generic Name

Ibrutinib

Rx Only

Dosage Forms

Capsule

Usage

Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), previously treated mantle cell lymphoma, Waldenström macroglobulinemia

Pregnancy Category D

Dosing

- CLL/SLL, Waldenström macroglobulinemia: 420 mg oral once daily
- Previously treated mantle cell lymphoma: 560 mg oral daily
- Hepatic dosage adjustment:
  - Mild impairment (Child-Pugh class A): Reduce to 140 mg oral once daily
  - Moderate and severe impairment (Child-Pugh class B and C): Avoid use

Adverse Reactions: Most Common

Diarrhea, fatigue, peripheral edema, bruising, nausea, vomiting, rash, increased uric acid, thrombocytopenia, neutropenia, anemia, transient lymphocytosis, upper respiratory infection

Adverse Reactions: Rare/Severe/Important

Atrial fibrillation, bleeding (gastrointestinal; hematuria; postprocedural, intracranial hemorrhage; subdural hematoma), renal toxicity

Major Drug Interactions

Drugs Affecting Ibrutinib

- Moderate and strong CYP3A4 inhibitors: Increases effects
- Moderate and strong CYP3A4 inducers: Decreases effects
- St John's wort: Decreases serum concentration

Ibrutinib's Effect on Other Drugs

- Antiplatelets: Increases risk of bleeding
- Anticoagulants: Increases risk of bleeding
- P-glycoprotein/ABCB1 substrates: Increases effects
- Vaccines: Decreases effects

Counseling Points

- Swallow capsules whole
- Take irrespective of meals with a full glass of water
- Avoid grapefruit, grapefruit juice, and Seville oranges as these may increase ibrutinib exposure
- Women of childbearing age should avoid pregnancy during therapy and for 1 month after treatment discontinuation
- No live virus vaccines should be given during therapy

Key Points

- Consider holding ibrutinib for 3 to 7 days prior to and after surgery, depending on the procedure type and risk of bleeding

- Dose adjustments needed if used with moderate or CYP3A4 inhibitors or inducers
- Avoid concurrent use with antiplatelets and anticoagulants

◉ Imatinib

Brand Name
Gleevec

Generic Name
Imatinib

Rx Only

Dosage Form
Tablet

Usage
Gastrointestinal stromal cell tumor, chronic myelogenous leukemia, Ph-positive acute lymphoblastic leukemia, dermatofibrosarcoma protuberans, hypereosinophilic syndrome, myelodysplastic disease, desmoid tumors, aggressive systemic mastocytosis with eosinophilia

Pregnancy Category D

Dosing
- Adults: 400 mg daily; up to 800 mg daily in divided doses
- Children: 260–340 mg/m^2 daily; maximum of 600 mg daily
- Renal dosage adjustment:
  - Mild impairment: No adjustment
  - Moderate impairment of CrCl 20–39 ml/min: Administer 50% of dose
  - Severe impairment of CrCl < 20 ml/min: Use not recommended
- Hepatic dosage adjustment:
  - Mild to moderate impairment: No adjustment
  - Severe impairment: Reduce dose by 25%

Adverse Reactions: Most Common
Fluid retention, nausea, diarrhea, rash, leukopenia, thrombocytopenia, anemia, myalgias, arthralgias, muscle cramps

Adverse Reactions: Rare/Severe/Important
Hepatotoxicity, heart failure, severe bullous dermatologic reactions, hemorrhage

Major Drug Interactions
Drugs Affecting Imatinib
- Azole antifungals: Increase serum concentration
- Lansoprazole: Enhances the dermatologic adverse effects of imatinib; monitoring is necessary

Imatinib's Effect on Other Drugs
- Carbamazepine: Inhibits carbamazepine metabolism, increasing carbamazepine concentrations and toxicity
- Digoxin: Decreases absorption
- Codeine: Diminishes therapeutic effect due to inhibition of codeine conversion to active metabolite
- Colchicine, cyclosporine, fentanyl: Serum levels may increase
- Fludarabine: Therapeutic effects may be diminished
- Simvastatin: Metabolism may be reduced
- Tamoxifen: Therapeutic effects may be diminished
- Tramadol: Therapeutic effects may be diminished
- Warfarin: Bleeding effects may be increased

Counseling Points
- Take with food and/or large glass of water
- Avoid eating grapefruit or drinking grapefruit juice
- Report any fevers, bleeding, bruising, or flank pain
- Report any shortness of breath

Key Points
- Edema can progress to pulmonary edema
- Edema is worse in the elderly
- Food may reduce GI irritation

VINCA ALKALOIDS

Introduction
Vinca alkaloids are derived from natural plant sources and are used to treat hematologic and solid tumors. They are usually part of a combination regimen, frequently in pediatric malignancies. The class is known for its neurotoxicity, with vincristine having the highest incidence and grade, limiting the possible dosing.

Mechanism of Action for the Drug Class
Vinca alkaloids prevent microtubule assembly, thereby preventing cell mitosis and ultimately causing cell death

Members of the Drug Class
In this section: Vincristine
Others: Vinblastine, vinorelbine

◉ Vincristine

Brand Name
Oncovin

Generic Name
Vincristine

Rx Only

Dosage Form
Injection

Usage
Acute lymphocytic leukemia, Hodgkin's lymphoma, *non-Hodgkin's lymphoma, Wilms' tumor,* neuroblastoma, rhabdomyosarcoma

Pregnancy Category D

Dosing
- Individual protocols specify dosing for specific indications and institutions
- Adult IV: 2 mg max per dose
- Children:
  - ≤ 10 kg: 0.05 mg/kg once weekly
  - > 10 kg: 1.5–2 mg/m^2; frequency may vary based on protocol
- Hepatic dosage adjustment:
  - Total bilirubin greater than the upper limit of normal: Avoid use
  - Aspartate aminotransferase/alanine aminotransferase > 1.5 times the upper limit of normal concomitant with alkaline phosphatase > 2.5 times the upper limit of normal: Avoid use

Adverse Reactions: Most Common
Peripheral neuropathies, constipation, jaw pain, depression, confusion

Adverse Reactions: Rare/Severe/Important
Ileus, uric acid nephropathy

Major Drug Interactions
Drugs Affecting Vincristine
- CYP3A4 inhibitors: May increase toxicity
- CYP3A4 inducers: May decrease efficacy

Contraindications
Patients with demyelinating form of Charcot-Marie-Tooth syndrome

Counseling Points
- Constipation may occur, requiring laxative therapy
- Report any numbness and tingling in hands and feet
- Report any change in mental status
- Report any jaw pain

Key Points
- Extravasation can cause tissue necrosis
- IV use only: Vincristine should be clearly labeled "FOR IV USE ONLY – FATAL IF GIVEN BY OTHER ROUTES"
- Vincristine should be dispensed in a minibag or IV admixture instead of a syringe to prevent inadvertent intrathecal administration
- Dosing is usually capped at 2 mg per dose due to its neurotoxicity; any dose exceeding this should be questioned
- A liposomal formulation of vincristine (Marqibo) is available. The two formulations, however, are not interchangeable as they have different indications and dosing.
- If given on its own, it does not require antiemetics
- If given alone, it does not cause bone marrow suppression
- Jaw pain is more common with the first dose
- Use of laxatives can prevent constipation and possible ileus
- Avoid eye contamination

REVIEW QUESTIONS

1. Etoposide belongs to which of the following drug classes?
   a. Podophyllotoxins
   b. Vinca alkaloids
   c. Anthracyclines
   d. Proteasome Inhibitors

2. Ibuprofen must be avoided a couple of days before and after administration of which of the following antineoplastic drugs?
   a. Carboplatin
   b. Cyclophosphamide
   c. Vincristine
   d. Pemetrexed

3. Which of the following antineoplastic agents must be administered with prednisone to prevent mineralocorticoid excess?
   a. Abiraterone acetate
   b. Bicalutamide
   c. Etoposide
   d. Ibrutinib

4. Which of the following adverse effects of capecitabine is of most concern?
   a. Conjunctivitis
   b. Neurotoxicity
   c. Mucositis
   d. Hypertension

5. _____ is a rare but serious side effect associated with cisplatin.
   a. Cardiotoxicity
   b. Immune-mediated pneumonitis
   c. Ototoxicity
   d. Hypothyroidism

6. Nivolumab can be used for the management of which of the following malignancies?
   a. Ovarian cancer
   b. Glioblastoma multiforme
   c. Thyroid cancer
   d. Advanced renal cell carcinoma

7. Bortezomib belongs to which drug class?
   a. Tyrosine Kinase Inhibitors
   b. Immunomodulators
   c. Proteasome Inhibitors
   d. Topoisomerase Inhibitors

8. Which of the following antineoplastic agents requires blood pressure monitoring at each visit?
   a. Cetuximab
   b. Nivolumab
   c. Obinutuzumab
   d. Bevacizumab

9. Which of the following agents target Bruton Tyrosine Kinase (BTK)?
   a. Ibrutinib
   b. Erlotinib
   c. Imatinib
   d. Osimertinib

10. Which of the following antineoplastic agents can increase the serum concentration of warfarin, potentially leading to an increased risk of bleeding?
    a. Cytarabine
    b. Casodex
    c. Bortezomib
    d. Revlimid

11. Mesna may be used as a uroprotective agent for which of the following drugs?
    a. Cisplatin
    b. Cyclophosphamide
    c. Fluorouracil
    d. Methotrexate

12. Which of the following antineoplastic agents can be administered intrathecally?
    a. Bortezomib
    b. Vincristine
    c. Cytarabine
    d. Capecitabine

13. Which agent causes stabilization of the microtubules, ultimately inhibiting cellular replication?
    a. Erbitux
    b. Paclitaxel
    c. Carboplatin
    d. Methotrexate

14. Which of the following agents requires renal dosage adjustments?
    a. Tamoxifen
    b. Vincristine
    c. Cisplatin
    d. Rituxan

15. An echocardiogram should be obtained prior to initiation of which of the following antineoplastic agents?
    a. Trastuzumab
    b. Cisplatin
    c. Nivolumab
    d. Docetaxel

16. Which of the following agents is indicated for mantle cell lymphoma?
    a. Cetuximab
    b. Lenalidomide
    c. Fluorouracil
    d. Oxaliplatin

17. Which of the following requires women of childbearing age to be on adequate birth control?

- **a.** Cyclophosphamide
- **b.** Rituximab
- **c.** Tamoxifen
- **d.** Adriamycin

18. Which of the following monoclonal antibodies targets the CD20 surface antigen on B-cells?

- **a.** Cetuximab
- **b.** Rituximab
- **c.** Nivolumab
- **d.** Bevacizumab

19. Patients with a known deficiency of dihydropyrimidine dehydrogenase (DPD) should not receive which of the following antineoplastic agents?

- **a.** Capecitabine
- **b.** Irinotecan
- **c.** Cytarabine
- **d.** Bortezomib

20. Zytiga is the brand name for which of the following agents?

- **a.** Ibrutinib
- **b.** Bicalutamide
- **c.** Crizotinib
- **d.** Abiraterone acetate

21. One of the most common side effects associated with letrozole is _____.

- **a.** Mucositis
- **b.** Contact dermatitis
- **c.** Peripheral neuropathy
- **d.** Hot flashes

22. What agent has both nononcologic and oncologic indications?

- **a.** Cisplatin
- **b.** Trexall
- **c.** Ibrutinib
- **d.** Docetaxel

23. The management of immune-mediated toxicities associated with nivolumab may involve which of the following?

- **a.** Folic acid
- **b.** Corticosteroids
- **c.** Leucovorin
- **d.** Thiamine

24. Hepatotoxicity is associated with which of the following agents?

- **a.** Opdivo
- **b.** Herceptin
- **c.** Letrozole
- **d.** Carboplatin

25. Which of the following agents may be used to manage extravasations involving Adriamycin?

- **a.** Leucovorin
- **b.** Dexrazoxane
- **c.** Hyaluronidase
- **d.** Corticosteroids

26. What class of antineoplastic agents typically interact with strong CYP3A4 inhibitors and inducers?

- **a.** Aromatase inhibitors
- **b.** Tyrosine kinase inhibitors
- **c.** Monoclonal antibodies
- **d.** Platinum compounds

27. Patients started on vincristine should be counseled to report which of the following side effects?

- **a.** Cough
- **b.** Numbness
- **c.** Headaches
- **d.** Diarrhea

28. What counseling points should be emphasized in a patient taking erlotinib?

- **a.** Erlotinib must be taken on an empty stomach
- **b.** Erlotinib can be taken with grapefruit juice
- **c.** Erlotinib must be taken with oral prednisone 10 mg daily
- **d.** Erlotinib tablets must be stored in the refrigerator

29. Which of the following statements is true regarding cyclophosphamide?

- **a.** Cyclophosphamide can be administered intrathecally
- **b.** Cyclophosphamide requires renal dosage adjustments in patients with mild renal impairment
- **c.** Oral cyclophosphamide should be taken early in the day
- **d.** Cyclophosphamide is commonly associated with ototoxicity

30. Which of the following agents is available in both oral and intravenous formulations?

- **a.** Topotecan
- **b.** Imatinib
- **c.** Herceptin
- **d.** Tamoxifen

CHAPTER 5

Cardiovascular Agents

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ALPHA-1 ADRENERGIC BLOCKERS

Introduction

Alpha-1 adrenergic blockers are used in the treatment of hypertension. Drugs in this class are usually not the first-line agent of choice because more effective agents are available. They are more commonly used in the treatment of benign prostatic hyperplasia (BPH).

Mechanism of Action for the Drug Class

Alpha-1 adrenergic blockers cause vasodilation by selectively blocking postsynaptic alpha-1 adrenergic receptors, resulting in dilation of both peripheral arterioles and veins.

Members of the Drug Class

In this section: Doxazosin, terazosin
Others: Phenoxybenzamine, phentolamine, prazosin

Rx Only for the Drug Class

Usage for the Drug Class

Treatment of hypertension, *BPH*

Pregnancy Category C for the Drug Class

Adverse Reactions for the Drug Class: Most Common

Dizziness, headache, orthostatic hypotension, syncope

Adverse Reactions for the Drug Class: Rare/Severe/Important

Intraoperative floppy iris syndrome (in patients undergoing cataract surgery), priapism, symptoms of angina

Major Drug Interactions for the Drug Class

Drugs Affecting Alpha-1 Adrenergic Blockers

Concomitant antihypertensive agents and phosphodiesterase-5 inhibitors: Additive hypotension

Alpha-1 Adrenergic Blocker Effects on Other Drugs

Antihypertensive agents: Additive hypotension

Essential Monitoring Parameters

Orthostatic hypotension, urinary symptoms

Counseling Points for the Drug Class

- Those drugs may cause dizziness or drowsiness (take at night to avoid)
- Use caution when getting up from a sitting or lying down position
- May require 1 to 2 weeks of therapy before improvement of BPH symptoms

Doxazosin

Brand Names

Cardura, Cardura XL

Generic Name

Doxazosin

Dosage Forms

Tablet, extended-release tablet

Dosing

- BPH: Immediate release: initial dose: 1 mg daily (maximum for BPH is 8 mg)
- BPH: Extended release: Initial dose: 4 mg once daily (maximum for BPH is 8 mg)
- Hypertension: Immediate release: Initial dose: 1 mg daily (maximum for hypertension is 16 mg)

Counseling Point

Do not crush, split, or chew the XL formulation

Key Points

- Although indicated for the treatment of hypertension, doxazosin is not often used as a first-line agent. It is more commonly used for the treatment of BPH. Watch for signs of orthostatic hypotension and signs of dizziness.
- The extended-release formula is a nondeformable matrix that is expelled in the stool. Be cautious when

using for patients with known stricture/narrowing of the GI tract.

Terazosin

Brand Name
Hytrin

Generic Name
Terazosin

Dosage Form
Capsule

Dosing
- BPH: Initial dose: 1 mg at bedtime (maximum for BPH is 20 mg)
- HTN: Initial dose: 1 mg at bedtime (maximum for HTN is 20 mg)

Key Points
- Although indicated for the treatment of hypertension, terazosin is not often used as a first-line agent. It is more commonly used for the treatment of BPH.
- Monitor for orthostatic hypotension and signs of dizziness.

ALPHA-2 ADRENERGIC AGONISTS

Introduction
The alpha-2 adrenergic agonists are used for the treatment of hypertension, although usually not as a first-line agent of choice. They also have many unlabeled uses. Clonidine, which is used for the treatment of hypertension, can cause significant rebound hypertension, if stopped abruptly.

Mechanism of Action for the Drug Class
The stimulation of alpha-2 adrenergic receptors in the brain stem by those agents results in reduced sympathetic outflow from the CNS and a decrease in peripheral resistance, renal vascular resistance, heart rate, and blood pressure.

Members of the Drug Class
In this section: Clonidine
Others: Dexmedetomidine, guanabenz, guanfacine, methyldopa

Clonidine

Brand Names
Catapres, Catapres-TTS-1, Catapres-TTS-2, Catapres-TTS-3, Duraclon, Kapvay

Generic Name
Clonidine

Rx Only

Dosage Forms
Tablet, transdermal patch, injection (epidural solution)

Usage
Hypertension, alcohol withdrawal, attention deficit hyperactivity disorder, cancer pain (epidural infusion), opioid or nicotine withdrawal, impulse control disorder, menopausal flushing (hot sweats), severe pain, tic disorder

Pregnancy Category C

Dosing
- Initial dose for hypertension:
  - Tablet: 0.1 mg twice daily
  - Transdermal: Start with Catapres-*TTS-1* (0.1 mg/24 hour) applied once every 7 days
  - May need to overlap oral therapy for 1–2 days when initiating transdermal
- Dosing adjustments
  - Tablet: Can increase in weekly intervals by 0.1 mg to a maximum dose of 2.4 mg daily. Can give in 2–4 daily doses.
  - Transdermal: Increase in 1- to 2-week intervals

Adverse Reactions: Most Common
CNS depression, constipation, dry mouth, dizziness, drowsiness, orthostatic hypotension

Adverse Reactions: Rare/Severe/Important
AV block, bradycardia, contact dermatitis (transdermal)

Major Drug Interactions
Drugs Affecting Clonidine
- Concomitant antihypertensive agents: Additive hypotension
- Tricyclic antidepressants: Decrease hypotensive effects
- Beta blockers: Additive bradycardia. Discontinuation of clonidine during concurrent use of a beta blocker may increase the risk of clonidine-withdrawal hypertensive crisis. It is preferred to discontinue the beta blocker several days prior to clonidine discontinuation.
- CNS depressants: Additive CNS effects

Clonidine's Effect on Other Drugs

- Cyclosporine: Increases levels

Essential Monitoring Parameters

Blood pressure, mental status, heart rate

Counseling Points

- Do not stop clonidine abruptly because it may cause rebound hypertension and other withdrawal symptoms (agitation, headache, tremor)
- Apply transdermal patch weekly to clean, hairless area of upper outer arm or chest and rotate site weekly
- Oral therapy and transdermal therapy may overlap for 1 to 2 days until the full effect of transdermal therapy occurs
- The transdermal patch may contain metal; must remove before an MRI

Key Points

- **Black Box Warning:**
  - Must dilute concentrated epidural injectable (500 mcg/ml) solution prior to use. Epidural clonidine is not recommended for perioperative, obstetric, or postpartum pain due to risk of hemodynamic instability.
- Clonidine is a very effective blood pressure–lowering agent. It is often added to other antihypertensive therapies in patients with resistant hypertension. The risk of rebound hypertension is high if the patient discontinues clonidine abruptly.
- The transdermal route takes 2 to 3 days for full therapeutic effect.
- Clonidine is commonly used for a variety of indications other than the treatment of hypertension.

ADRENERGIC AGONISTS

Introduction

The adrenergic agonist class of drugs includes agents that stimulate alpha-1 and/or beta-1 receptors. Some agents work on either receptor, whereas some work on both, resulting in vasoconstriction, increased cardiac contractility, or both. Those agents are only used in hospital settings for critically ill patients with severe hypotension, cardiogenic shock, and acute decompensated heart failure, who require close monitoring.

Members of the Drug Class

In this section: Dobutamine, dopamine, epinephrine, norepinephrine, phenylephrine

◉ Dobutamine

Brand Name

Dobutrex

Generic Name

Dobutamine

Rx Only

Mechanism of Action

A synthetic catecholamine that stimulates beta-1 receptors, resulting in increased contractility (positive inotrope) and heart rate. Hemodynamic effects include increased cardiac output and stroke volume, with minimal lowering of blood pressure.

Dosage Forms

IV (injection and premixed infusion)

Usage

Cardiogenic shock/severe decompensated heart failure, stress echocardiography

Pregnancy Category B

Dosing

- Initial dose: 2.5 µg/kg/min
- Dosage adjustment: Up to 2.5 µg/kg/min every 10 minutes; doses of up to 40 µg/kg/min may be required, although benefit beyond 20 µg/kg/min not likely

Adverse Reactions: Most Common

Increased heart rate/tachyarrhythmia

Adverse Reactions: Rare/Severe/Important

Ventricular arrhythmias

Major Drug Interactions

Drugs Affecting Dobutamine

- Negative inotropes (beta blockers, verapamil/diltiazem): Decrease efficacy
- IV drugs: Check for compatibility when infusing through same line

Essential Monitoring Parameters

Blood pressure, heart rate, cardiac output/cardiac index, ECG

Key Points

- Only indicated for use in patients with severely decompensated heart failure and reduced cardiac output. Its use in stable heart failure patients is associated with increased mortality.
- Concomitant administration of a beta blocker may decrease effectiveness of dobutamine in decompensated heart failure as it relies on beta-1 receptors for its mechanism of action.
- Close hemodynamic monitoring is necessary

Dopamine

Brand Name
None

Generic Name
Dopamine

Rx Only

Mechanism of Action
Effects are dose related and dependent on patient clinical status. Low doses (1–5 µg/kg/min) stimulate dopaminergic receptors, resulting in vasodilation of renal, mesenteric, coronary, and intracerebral vasculature. Intermediate doses (5–10 µg/kg/min) stimulate beta-1 receptors, causing increased myocardial contractility and cardiac output (positive inotrope). High rates of infusion (>10 µg/kg/min) stimulate alpha-receptors, causing vasoconstriction and increased blood pressure.

Dosage Form
IV (injection and premixed infusion)

Usage
Adjunct treatment of shock (cardiac decompensation, septic), symptomatic bradycardia or heart block

Pregnancy Category C

Dosing
- Low dose: 1–5 µg/kg/min
- Intermediate dose: 5–10 µg/kg/min
- High dose: 10–20 µg/kg/min
- Very high dose: 20–50 µg/kg/min

Adverse Reaction: Most Common
Increased heart rate/tachyarrhythmia

Adverse Reactions: Rare/Severe/Important
Ventricular arrhythmias, limb necrosis (with higher rates of infusion)

Major Drug Interactions
Drugs Affecting Dopamine
- Negative inotropes (beta blockers, verapamil/diltiazem): Decrease efficacy
- Vasodilators: Decrease efficacy
- IV drugs: Check for compatibility when infusing through same line

Contraindications
Pheochromocytomas, uncorrected tachyarrhythmias, ventricular fibrillation

Essential Monitoring Parameters
Blood pressure, heart rate, cardiac output/cardiac index, ECG

Key Points
- **Black Box Warning:**
  - If extravasation occurs, infiltrate area with diluted phentolamine with a fine hypodermic needle. Phentolamine should be administered as soon as possible after extravasation is noted to prevent sloughing/necrosis.
- Dopamine is primarily used as adjunctive therapy in patients with hemodynamic compromise/shock. Doses used depend on the goal of therapy, and patient response varies, depending on the clinical situation.
- Close hemodynamic monitoring and dose adjustment is necessary

Epinephrine

Brand Name
Adrenalin, EpiPen, EpiPen Jr, Auvi-Q

Generic Name
Epinephrine

Rx Only

Mechanism of Action
Epinephrine is a sympathomimetic catecholamine with numerous uses, based on various mechanisms of action. Epinephrine is a very potent activator of alpha-receptors, resulting in vasoconstriction and decreased vascular permeability. It also stimulates beta-1 and beta-2 receptors, resulting in relaxation of bronchial smooth muscle and stimulation of heart rate and cardiac contractility.

Dosage Forms
Injection (vials, prefilled syringe, and auto-injectors),

Usage
Advanced cardiovascular life support (ACLS; ventricular fibrillation/pulseless ventricular tachycardia, pulseless electric activity, asystole), *anaphylactic reactions,* bradycardia, bronchospasms/asthma/wheezing, shock/hypotension

Pregnancy Category C

Dosing
- ACLS:
  - IV: 1 mg every 3 to 5 minutes until return of spontaneous circulation
  - Endotracheal administration: 2–2.5 mg every 3 to 5 minutes
- Anaphylaxis:
  - IM (preferred)/SubQ: 0.2–0.5 mg
  - IM/SubQ (auto-injector): 0.3 mg; if symptoms persist, may repeat dose
  - IV: 0.1 mg
- Shock/hypotension:
  - Continuous infusion: 1–10 µg/min

Adverse Reactions: Most Common
Increased heart rate/tachyarrhythmia, headache, hyperglycemia, tremor

Adverse Reactions: Rare/Severe/Important
Ventricular arrhythmias, limb necrosis (with higher rates of infusion), worsening coronary artery disease or cerebrovascular disease

Major Drug Interactions
Drugs Affecting Epinephrine
- Negative inotropes (beta blockers, verapamil/diltiazem): Decrease efficacy
- Vasodilators: Decrease efficacy
- IV drugs: Check for compatibility when infusing through same line

Essential Monitoring Parameters
Blood pressure, heart rate, cardiac output/cardiac index, ECG

Counseling Points
- Autoinjectors should be administered into the anterolateral aspect of the middle third of the thigh and can be administered through clothing, if necessary
- A second dose should always be available and can be administered if response to first dose is inadequate. More than two doses should only be administered under medical care.

Key Points
- Epinephrine is used for a variety of acute indications, often in situations requiring immediate treatment. Its actions on alpha and beta receptors result in effective treatment of anaphylaxis, wheezing, and arrhythmias/circulatory shock.
- Close hemodynamic monitoring and dose adjustment is necessary when administering as continuous infusion

◉ Norepinephrine

Brand Name
Levophed

Generic Name
Norepinephrine

Rx Only

Mechanism of Action
Stimulates alpha receptors, resulting in vasoconstriction, and beta receptors, resulting in increased heart rate and cardiac contractility

Dosage Form
Injection (vials, premixed infusion)

Usage
Shock/hypotension

Pregnancy Category C

Dosing
- Initial dose: 8–12 µg/min
- Dosage adjustment: Up to 20 µg/min
- Weight-based dosing: 0.01–3 µg/kg/min

Adverse Reactions: Most Common
Increased heart rate/tachyarrhythmia, headache, anxiety

Adverse Reactions: Rare/Severe/Important
Ventricular arrhythmias, limb/skin necrosis

Major Drug Interactions
Drugs Affecting Norepinephrine
- Negative inotropes (beta blockers, verapamil/diltiazem): Decrease efficacy
- Vasodilators: Decrease efficacy
- IV drugs: Check for compatibility when infusing through the same line

Essential Monitoring Parameters
Blood pressure, heart rate, cardiac output/cardiac index, ECG

Key Points
- **Black Box Warning:**
  - If extravasation occurs, infiltrate area with diluted phentolamine with a fine hypodermic needle. Phentolamine should be administered as soon as possible after extravasation is noted to prevent sloughing/necrosis.
- Norepinephrine is used primarily to increase blood pressure in patients with hypotension and shock.
- Close hemodynamic monitoring and dosage adjustment is necessary.

◉ Phenylephrine

Brand Names
Numerous OTC combination products, including, Sudafed PE, Little Colds, Neo-Synephrine, Nasal Four, Mydfrin

Generic Name
Phenylephrine

Rx (IV) and OTC (Oral, Ophthalmic, Nasal Spray)

Mechanism of Action
Phenylephrine is a sympathomimetic agent with only alpha-receptor activity. Stimulation of alpha-receptors results in systemic arterial vasoconstriction, resulting in increased blood pressure. Vasoconstriction results in reflex bradycardia and decreased cardiac output in patients with heart failure.

Dosage Forms
Injection, liquid solution, tablet, nasal spray, ophthalmic

Usage
Hypotension/shock (IV only), *decongestant* (oral, nasal spray), vasoconstrictor in regional anesthesia

Pregnancy Category C

Dosing
- IV: 100–180 µg/min up to 300 µg/min
- Weight-based dosing: 0.5–9 µg/kg/min
- Oral: 10 mg every 4 hours as needed

Adverse Reactions: Most Common
Hypertension, reflex bradycardia, headache, tremor

Adverse Reactions: Rare/Severe/Important
Limb necrosis (with higher rates of infusion), worsening coronary artery disease, or cerebrovascular disease

Major Drug Interactions
Drugs Affecting Phenylephrine
- Vasodilators: Decrease efficacy
- IV drugs: Check for compatibility when infusing through the same line

Contraindications
Oral: Cardiovascular disease, hypertension, narrow-angle glaucoma, BPH; use within 14 days of MAOI therapy

Essential Monitoring Parameters
Blood pressure, heart rate, cardiac output/cardiac index

Counseling Point
When using for self-treatment (OTC), notify healthcare provider if symptoms do not resolve within 7 days

Key Points
- Phenylephrine is a potent vasoconstrictor used intravenously in the treatment of hypotension and shock. Oral formulations, often in combination with other ingredients, exist for treatment of congestion.
- Close hemodynamic monitoring and dosage adjustment are necessary when administering as continuous infusion
- The properties of phenylephrine administered intravenously compared with administration via other routes are so different that they resemble different drugs. The oral and nasal spray formulations of phenylephrine do have some systemic absorption, although their systemic effects are minimal compared with the IV form.
- Oral OTC preparations should be avoided in patients with hypertension, narrow-angle glaucoma, BPH; use within 14 days of MAOI therapy

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Introduction
The angiotensin-converting enzyme (ACE) inhibitors are widely used for various cardiovascular diseases. They are effective for the treatment of hypertension and are the foundation of therapy for heart failure with reduced ejection fraction (HFrEF). In addition, they are used for the prevention and treatment of diabetic nephropathy.

Mechanism of Action for the Drug Class
Those agents act primarily through suppression of the renin–angiotensin–aldosterone system. They inhibit ACE, thereby inhibiting the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. Angiotensin II also promotes the release of aldosterone, which causes sodium and water retention.

Members of the Drug Class
In this section: Benazepril, captopril, enalapril/enalaprilat, fosinopril, lisinopril, quinapril, ramipril
Others: Moexipril, perindopril, trandolapril

Rx Only for the Drug Class

Usage for the Drug Class
Diabetic nephropathy, heart failure, hypertension, left ventricular dysfunction after myocardial infarction, acute myocardial infarction

Pregnancy Category D for the Drug Class

Adverse Reactions for the Drug Class: Most Common
Hypotension, hyperkalemia, cough, taste disorder (captopril)

Adverse Reactions for the Drug Class: Rare/Severe/Important
Angioedema (contraindication for use), azotemia, and renal failure in susceptible patients (e.g., volume depleted); neutropenia/agranulocytosis (captopril); avoid use in patients with bilateral renal artery stenosis, hepatic syndrome

Major Drug Interactions for the Drug Class

Drugs Affecting ACE Inhibitors

- Concomitant antihypertensive agents: Additive hypotension
- Angiotensin II receptor blockers, potassium-sparing diuretics, trimethoprim/sulfamethoxazole: Increase risk of hyperkalemia
- Angiotensin receptor blockers: Use in combination with ACE inhibitors should be avoided due to increased risk of hyperkalemia
- Diuretics: May potentiate renal insufficiency in volume-depleted patients
- NSAIDs: Reduce hypotensive effect of ACE inhibitors

ACE Inhibitor Effects on Other Drugs

- Antihypertensive agents: Additive hypotension
- Cyclosporine: Increases nephrotoxicity
- Lithium: Increases serum levels
- Potassium-sparing diuretics, potassium supplements: May cause elevated potassium levels

Contraindication for the Drug Class

Angioedema with previous ACE inhibitor use

Essential Monitoring Parameters for the Drug Class

Renal function (serum creatinine), potassium, cough, angioedema, blood pressure

Counseling Points for the Drug Class

- Laboratory work will be needed periodically to monitor therapy (potassium, serum creatinine)
- Seek help immediately if swelling in the face, lips, tongue, or throat occurs
- Avoid salt substitutes containing potassium
- Notify a healthcare professional if a cough develops
- Women: Notify your physician if pregnancy is suspected

Key Points for the Drug Class

- ACE inhibitors are widely used for the treatment of hypertension, HFrEF, and diabetic nephropathy
- Monitoring parameters should include renal function (serum creatinine), potassium, cough, angioedema, and blood pressure
- Those agents should not be used if pregnant

Benazepril

Brand Name

Lotensin

Generic Name

Benazepril

Dosage Form

Tablet

Dosing

- Initial dose: 10 mg daily
- Dosage adjustment:
  - Up to 40 mg daily in 1 to 2 divided doses
  - Doses up to 80 mg daily may be tried, although increased efficacy using doses beyond 40 mg is limited
- Renal dosage adjustment: If CrCl < 30 ml/min, consider starting at lower doses (5 mg daily)

Captopril

Brand Name

Capoten (no longer available)

Generic Name

Captopril

Dosage Form

Tablet

Dosing

- Acute hypertension
  - Oral: 25 mg, may repeat as needed
- HFrEF
  - Initial dose: 6.25 mg 3 times daily, target dose 50 mg 3 daily
- Hypertension
  - Initial dose: 25 mg 2 to 3 times daily
  - Dosage adjustment: Up to 450 mg daily in three divided doses
- Renal dosage adjustment: Consider starting at a lower doses

Key Points

- The use of captopril is typically used for urgent acute hypertension
- It is often limited to the inpatient setting because it is administered three times a day
- Other ACE inhibitors with more convenient dosing regimens (once or twice daily) are preferentially used

Enalapril/Enalaprilat

Brand Name

Vasotec, Epaned

Generic Name

Enalapril/Enalaprilat

Dosage Forms

Tablet, solution, injection (as enalaprilat)

Dosing

- Hypertension
  - Oral (initial dose): 5 mg once daily
  - IV (Initial dose): 1.25 mg every 6 hours
- HFrEF
  - Oral (initial dose): 2.5 mg twice daily, target dose 10–20 mg twice daily
- Dosage adjustment:
  - Renal dosage adjustment: Consider starting at lower doses

- IV to oral conversion:
  - 0.625 mg IV every 6 hours to 2.5 mg PO daily
  - 1.25 mg IV every 6 hours to 5 mg PO daily

Key Points

- Enalaprilat is a more potent activated form of enalapril with an extended half-life that is administered via IV
- It should be used cautiously because it can decrease blood pressure precipitously for prolonged periods of time

Fosinopril

Brand Name

Monopril (no longer available)

Generic Name

Fosinopril

Dosage Form

Tablet

Dosing

- HFrEF
  - Initial: 5 to 10 mg once daily, target dose 40 mg once daily
- Hypertension
  - Initial: 10 mg once daily
- Dosage adjustment: Up to 40 mg daily in 1 to 2 doses

Lisinopril

Brand Names

Prinivil, Zestril, Qbrelis

Generic Name

Lisinopril

Dosage Form

Tablet, Solution

Dosing

- HFrEF
  - Initial: 2.5–5 mg once daily, target dose 20–40 mg once daily
- Hypertension
  - Initial dose: 5–10 mg daily
- Renal dosage adjustment: Consider starting at lower dose (2.5 mg)

Quinapril

Brand Name

Accupril

Generic Name

Quinapril

Dosage Form

Tablet

Dosing

- HFrEF
  - Initial: 5 mg twice daily, target dose 20 mg twice daily
- Hypertension
- Initial dose: 10–20 mg daily
- Renal dosage adjustment: Consider starting at lower dose

Ramipril

Brand Name

Altace

Generic Name

Ramipril

Dosage Forms

Capsule

Dosing

- Initial dose: 2.5 mg daily
- Dosage adjustment: Up to 20 mg daily in 1 to 2 divided doses
- Renal dosage adjustment: Consider starting at lower dose

Key Point

Ramipril is also indicated to reduce the risk of myocardial infarction, stroke, and death from cardiovascular causes in patients who are at increased risk of those events.

ANGIOTENSIN II RECEPTOR BLOCKERS

Introduction

Angiotensin II receptor blockers (ARBs) are widely used for the treatment of cardiovascular diseases. They are primarily used for the treatment of hypertension and as an alternative to ACE inhibitors for the treatment of HFrEF and diabetic nephropathy. Although they also work along the renin–angiotensin–aldosterone system, they have an advantage over ACE inhibitors in that they do not cause cough, as ACE inhibitors do. Although the agents in this class are largely similar, there are differences in their pharmacokinetics and their approved indications, depending on the disease states in which they have been studied.

Mechanism of Action for the Drug Class

Those agents suppress the renin–angiotensin–aldosterone system. They block the binding of angiotensin II to the AT1 receptor, thereby inhibiting the effects of angiotensin II, a potent vasoconstrictor that also promotes the release of aldosterone and causes sodium and water retention.

Members of the Drug Class

In this section: Irbesartan, losartan, olmesartan, valsartan
Others: Azilsartan, candesartan, eprosartan, telmisartan

Rx Only for the Drug Class

Usage for the Drug Class

Hypertension, *diabetic nephropathy*, *heart failure* (select ARBs), myocardial infarction

Pregnancy Category D for the Drug Class

Adverse Reactions for the Drug Class: Most Common

Hyperkalemia, hypotension

Adverse Reactions for the Drug Class: Rare/Severe/Important

Increased serum creatinine, angioedema

Major Drug Interactions for the Drug Class

Drugs Affecting ARBs

- Concomitant antihypertensive agents: Additive hypotension
- Potassium supplements and potassium-sparing diuretics: Potential additive increases in potassium
- ACE inhibitors, potassium-sparing diuretics, trimethoprim/sulfamethoxazole: Increases risk of hyperkalemia
- ACE inhibitor: Use in combination with ARBs should be avoided due to increased risk of hyperkalemia

ARBs' Effects on Other Drugs

Lithium: May reduce elimination

Contraindications

Angioedema with previous ARB use

Essential Monitoring Parameters for the Drug Class

Renal function (serum creatinine), potassium, angioedema (rare), blood pressure

Counseling Points for the Drug Class

- Laboratory work will be needed periodically to monitor therapy (potassium, serum creatinine)
- Women: Notify your physician if pregnancy is suspected

Key Points for the Drug Class

- ARBs are used widely for the treatment of cardiovascular diseases
- They are often used in patients intolerant of ACE inhibitors who have heart failure (candesartan, losartan, valsartan only)

Irbesartan

Brand Name

Avapro

Generic Name

Irbesartan

Dosage Form

Tablet

Dosing

- Initial dose: 75–150 mg daily
- Dosage adjustment: Up to 300 mg daily

Key Point

Not recommended for heart failure

Losartan

Brand Name

Cozaar

Generic Name

Losartan

Dosage Form

Tablet

Dosing

- Initial dose: 25–50 mg daily
- Dosage adjustment: Up to 100 mg daily in 1–2 divided doses

Key Point

May be used off label for heart failure

Olmesartan Medoxomil

Brand Name

Benicar

Generic Name

Olmesartan medoxomil

Dosage Form

Tablet

Dosing

- Initial dose: 20 mg once daily
- Dosage adjustment: Up to 40 mg daily

◉ Valsartan

Brand Name
Diovan

Generic Name
Valsartan

Dosage Form
Tablet

Dosing
- HFrEF
  - Initial dose: 40 mg twice daily, target dose 160 mg twice daily
- Hypertension
  - Initial dose: 80–160 mg daily
  - Dosage adjustment: Up to 320 mg daily in 1 to 2 divided doses

Key Point
Preferred ARB in patients with heart failure

ANTIANGINALS, RANOLAZINE

Introduction

Ranolazine is a unique agent whose exact mechanism of action is unknown. It does not rely on decreased heart rate or myocardial workload for its antianginal effects. It is used in patients with continued angina symptoms, despite maximum therapy with other antianginals or who cannot tolerate additional antianginal therapy due to low heart rate or blood pressure.

Mechanism of Action for the Drug Class

The exact mechanism of ranolazine is unknown. One possible mechanism is inhibition of the inward sodium channel in the ischemic myocardium, resulting in decreased calcium influx and decreased ventricular tension and oxygen consumption. Another postulated mechanism is that ranolazine inhibition of fatty acid oxygenation results in increased glucose oxidation and generation of more ATP per molecule of oxygen.

◉ Ranolazine

Brand Name
Ranexa

Generic Name
Ranolazine

Rx Only

Dosage Form
Extended-release tablet

Usage
Treatment of chronic angina

Pregnancy Category C

Dosing
- Initial dose: 500 mg twice daily
- Dosage adjustment: Up to 1000 mg twice daily
- Renal dosage adjustment: No specific recommendations; however, levels increase by 50% in patients with renal dysfunction

Adverse Reactions: Most Common
Dizziness, QTc prolongation

Adverse Reactions: Rare/Severe/Important
Torsade de pointes

Major Drug Interactions

Drugs Affecting Ranolazine
- Diltiazem, erythromycin, fluconazole, verapamil, and other moderate CYP3A4 inhibitors: Ranolazine dose should not exceed 500 mg twice daily
- Strong CYP3A4 inhibitors: Increased risk of QTc prolongation, avoid use
- CYP3A4 inducers: Decreased efficacy
- QTc-prolonging drugs: Increased risk of QTc prolongation

Ranolazine's Effect on Other Drugs
- Simvastatin: Dose should not exceed 20 mg daily
- Substrates of P-glycoprotein: Increases risk of toxicity

Contraindications
- Use with caution in patients with QTc prolongation.
- Contradicted for patients with any degree of hepatic cirrhosis and contraindicated with strong CYP3A4 inhibitors and inducers

Essential Monitoring Parameter

EKG (QTc interval), renal function, and potassium

Counseling Points

- Do not crush, break, or chew tablet
- Ranolazine should not be used to treat an acute angina episode

Key Points

- Ranolazine is used for the treatment of chronic angina symptoms. Because it does not affect heart rate or blood pressure, it is used when patients cannot tolerate other antianginal agents.
- EKG must be monitored closely because the QTc interval can be prolonged

ANTIARRHYTHMICS

Introduction

The use of antiarrhythmics in the United States have decreased substantially due to major adverse effects and the advanced technology of nonpharmacologic therapies, such as implantable cardiac-defibrillators (ICD) and ablation. Currently available antiarrhythmics are classified based on their electrophysiologic actions in altering cardiac conduction. This is known as the Vaughan–Williams Classification. This classification has been met with some criticism because it is incomplete, does not allow for the classification of other agents (digoxin), and many agents have properties of more than one drug class. Nonetheless, it is still used despite its shortcomings. The following sections will focus on amiodarone, digitalis glycosides, and sotalol; however, the Vaughan–Williams Classification is provided in **Table 5-1** for reference.

TABLE 5–1 Vaughan–Williams Classification

Class	Mechanism	Drug
Ia	Sodium and potassium channel blockers	• Quinidine • Procainamide • Disopyramide
Ib	Sodium channel blockers	• Lidocaine • Mexiletine
Ic	Sodium channel blockers	• Flecainide • Propafenone
II	Beta blockers	• Atenolol • Metoprolol
III	Potassium channel blockers	• Amiodarone • Dofetilide • Dronedarone • Sotalol • Ibutilide
IV	Calcium channel blockers	• Verapamil • Diltiazem

ANTIARRHYTHMICS, AMIODARONE

Introduction

Amiodarone is the most commonly used antiarrhythmic agent. It is used for rate and rhythm control of atrial fibrillation and to treat and prevent ventricular arrhythmias. It has a very long terminal half-life of approximately 2 months and a large volume of distribution and thus requires large loading doses administered over several weeks.

Mechanism of Action for the Drug Class

Amiodarone is considered a class III antiarrhythmic medication; however, it exhibits characteristics of all four Vaughan–Williams antiarrhythmic medication classes. Amiodarone slows intraventricular conduction by blocking sodium channels, slows the heart rate, and impedes AV node conduction by blocking beta-adrenergic receptors and calcium channels and prolongs atrial and ventricular repolarization by inhibiting potassium channels.

◉ Amiodarone

Brand Names

Cordarone, Pacerone, Nexterone

Generic Name

Amiodarone

Rx Only

Dosage Forms

Tablet, injection (vials and premixed infusion)

Usage

Atrial arrhythmias, life-threatening ventricular arrhythmias, prevention of postoperative atrial fibrillation in cardiothoracic surgery, prevention of ventricular arrhythmias in patients with internal cardioverter-defibrillators

Pregnancy Category D

Dosing

- Oral:
  - Loading dose of 800–1600 mg per day in divided doses for 1 to 3 weeks until adequate arrhythmia control is achieved (usually up to 10 g total)
  - Maintenance dose: 200–400 mg per day
- IV: Loading dose of 150–300 mg in 20–30 ml NS followed by 1 mg/min for 6 hours, then 0.5 mg/minute for 18 hours. Infusion can be continued for up to 4 weeks. Should switch to oral as soon as possible.

Adverse Reactions: Most Common

Bradycardia, corneal microdeposits, hypotension (more common with IV), hypothyroidism, nausea, vomiting (especially with higher doses), phlebitis (IV form), photosensitivity, prolonged QTc interval

Adverse Reactions: Rare/Severe/Important

Blue/gray skin discoloration, hyperthyroidism, liver toxicity, pulmonary toxicity

Major Drug Interactions

Drugs Affecting Amiodarone

- Drugs that prolong the QTc interval: May increase the QTc-prolonging effect of amiodarone
- Beta blockers, diltiazem, digoxin, and verapamil: May cause excessive atrioventricular block
- Cimetidine: Decreases metabolism
- Fluconazole, ketoconazole, voriconazole, itraconazole, posaconazole, azithromycin: Increase QT prolongation
- Darunavir, boceprevir, telaprevir, saquinavir, indinavir, nelfinavir, ritonavir, tipranavir, lopinavir, atazanavir, fosamprenavir: Increase risk of amiodarone cardiotoxicity

Amiodarone's Effect on Other Drugs

- Cyclosporine, tacrolimus, sirolimus: Increase levels
- Lovastatin, simvastatin: Increase risk of myopathy
- Digoxin: Increases levels
- Warfarin: Increases effects

Contraindications

Severe bradycardia, second- or third-degree AV block, cardiogenic shock

Essential Monitoring Parameters

Blood pressure, heart rate, pulmonary toxicity, liver function tests, thyroid, electrolytes (especially potassium and magnesium), ocular, skin (photosensitivity, SJS)

Counseling Points

- Take with food to decrease adverse GI effects
- Use sunscreen or stay out of sun to prevent burns
- Schedule regular blood work for thyroid and liver function
- Regular ophthalmic exams are necessary while on therapy

Key Points

- **Black Box Warning:**
  - Liver toxicity is common, but is usually mild with evidence of only increased liver enzymes; severe liver toxicity can occur and has been fatal in a few cases. Amiodarone can exacerbate arrhythmias by making them more difficult to tolerate or reverse. Pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis and abnormal diffusion capacity without symptoms) may occur. Amiodarone is only indicated for patients with life-threatening arrhythmias because of risk of substantial drug-related toxicity. Alternative therapies should be tried first before using amiodarone. Patients should be hospitalized when amiodarone is initiated.
- Although amiodarone is the most commonly used antiarrhythmic agent for atrial and ventricular arrhythmias, it should be reserved for patients with life-threatening arrhythmias because of its substantial toxicity
- Patients should be hospitalized for initiation of therapy and need to be monitored and counseled appropriately to limit toxicity

ANTIARRHYTHMICS, DIGITALIS GLYCOSIDES

Introduction

Digoxin is the only available digitalis glycoside and is one of the oldest medications used for the treatment of heart failure. Although it is still frequently used in heart failure, it is no longer a first-line choice because other agents (ACE inhibitors, beta blockers) have been proven more effective at reducing morbidity and mortality. Digoxin also has a role as a rate-control agent in the treatment of atrial fibrillation.

Mechanism of Action for the Drug Class

Inhibits sodium-potassium ATPase, leading to an increase in the intracellular concentration of sodium, thus stimulating sodium–calcium exchange. This increases the intracellular concentration of calcium, leading to increased contractility. Enhances vagal tone to directly suppress the atrioventricular node, which increases effective refractory period and decreases conduction velocity, resulting in decreased ventricular rate.

◉ Digoxin

Brand Names

Lanoxin, Digitek

Generic Name

Digoxin

Rx Only

Dosage Forms

Tablet, solution, injection

Usage

Heart failure (stage C), supraventricular arrhythmias

Pregnancy Category C

Dosing

- Atrial Fibrillation
  - Loading dose: 8–12 µg/kg ideal body weight (adjust for renal function). Average loading dose is 0.75–1 mg
  - Administration recommendations: Roughly half of the total loading dose administered as the first dose, with the remaining portion divided and administered every 6 to 8 hours initially
- Maintenance dose: 0.125–0.5 mg daily
- HFrEF
  - Loading dose: Generally not done
  - Maintenance dose: 0.125–0.5 mg daily
- Renal dosage adjustment (both loading and maintenance doses should be adjusted):
  - eGFR 10–50 ml/min: Administer 25% to 75% of dose or full dose every 36 hours
  - eGFR < 10 ml/min: Administer 10% to 25% of dose or full dose every 48 hours
  - End-stage renal disease: Reduce dose by 50%

Pharmacokinetic Monitoring

- Monitor levels after at least 6 hours following administration (usually prior to next dose)
- Obtain levels within 12 to 24 hours of initiating therapy if a loading dose is given or within 3–5 days following initiation if no loading dose is given
- Usual range 0.5–0.8 ng/dL for heart failure, 0.8–2 ng/dL for arrhythmias

Adverse Reactions: Most Common

Anorexia, diarrhea, dizziness, headache, nausea

Adverse Reactions: Rare/Severe/Important

Atrial tachycardia, AV dissociation, blurred or yellow vision, hallucinations, heart block, ventricular fibrillation/tachycardia

Major Drug Interactions

Drugs Affecting Digoxin

- Amiodarone (reduce digoxin dose by 50%), boceprevir, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone (reduce dose by 50%), erythromycin, fluconazole, itraconazole, quinidine, quinine, ritonavir, saquinavir, telaprevir, tetracyclines, verapamil: Increase digoxin serum levels
- Cholestyramine, colestipol, kaolin-pectin, sucralfate: Decrease digoxin therapeutic effects
- Diuretic-induced electrolyte decreases (potassium, magnesium) may predispose patients to digitalis-induced arrhythmias

Digoxin's Effect on Other Drugs

- Although beta blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV-node conduction may result in advanced or complete heart block

Essential Monitoring Parameters

Digoxin levels (to check for toxicity or compliance), renal function (serum creatinine), electrolytes (potassium, magnesium, calcium), heart rate/ECG periodically

Counseling Points

- Take digoxin at the same time every day
- Notify healthcare provider if any signs of toxicity occur (e.g., nausea, vomiting, blurry vision)

Key Points

- Although digoxin is not a first-line choice, it is often used in the treatment of symptomatic heart failure and atrial fibrillation

- Digoxin has a narrow therapeutic index, and dosing must be adjusted for renal function, weight, and heart failure status. Appropriate monitoring of renal function and electrolytes is necessary to avoid toxicity.
- Loading doses are typically not necessary for patients with heart failure

ANTIARRHYTHMICS, SOTALOL

Introduction

Sotalol has activity as both a beta blocker and as a class III antiarrhythmic. It is used for rate and rhythm control in patients with atrial fibrillation.

Mechanism of Action for the Drug Class

Sotalol has both nonselective beta-adrenergic blockade and class III antiarrhythmic actions that prolong cardiac action potential duration by inhibiting potassium channels

◉ Sotalol

Brand Names

Betapace, Betapace AF, Sorine, Sotylize

Generic Name

Sotalol

Rx Only

Dosage Forms

Tablet, IV solution

Usage

Atrial fibrillation, life-threatening ventricular arrhythmias

Pregnancy Category B

Dosing

- Initial dose:
  - Initiate treatment in a setting in which continual ECG monitoring is possible
  - Initial dose is based on CrCl:
    - CrCl > 60 ml/min: 80 mg twice daily
    - CrCl 40–60 ml/min: 80 mg daily
    - CrCl < 40 ml/min: Contraindicated
- Maintenance dose: Up to 160 mg twice daily

Adverse Reactions: Most Common

Bradycardia, dizziness, dyspnea, fatigue, QT interval prolongation (avoid if baseline QTc >450 msec; discontinue or decrease dose if QTc ≥ 500 msec during therapy)

Adverse Reactions: Rare/Severe/Important

Bronchospasm, heart block, torsades de pointes

Major Drug Interactions

Drugs Affecting Sotalol

- Calcium channel blockers: Increase bradycardia
- Digoxin: Increases proarrhythmic risk
- Drugs that prolong the QTc interval: Increase the QTc-prolonging effect of sotalol
- Fluconazole, itraconazole, ketoconazole, voriconazole: Increase risk of cardiotoxicity
- Antacids containing aluminum oxide or magnesium hydroxide: Reduces absorption

Sotalol's Effect on Other Drugs

Although calcium channel blockers and digoxin may be useful in combination with sotalol to control atrial fibrillation, their additive effects on AV node conduction may result in advanced or complete heart block.

Contraindications

Baseline QTc interval > 450 msec, long QT syndrome, heart failure (cardiogenic shock, uncontrolled heart failure), CrCl < 40 ml/min, hypokalemia, bradycardia, second- or third-degree AV block

Essential Monitoring Parameters

EKG (QTc interval), serum creatinine, magnesium, potassium, heart rate, blood pressure

Counseling Point

Routine blood tests are required to monitor renal function and electrolytes.

Key Points

- **Black Box Warning:**
  - Severe life-threatening ventricular tachycardia associated with QT interval prolongation. Do not initiate if baseline QTc interval is > 450 msec. If QTc interval prolongs to 500 msec or exceeds 500 msec during therapy, reduce the dose, prolong the interval between doses, prolong the duration of the infusion, or discontinue agent. Also, adjust dose based on CrCl.
- Initiation of therapy and dosage adjustments should occur in a hospital setting with continual monitoring
- Betapace and Betapace AF should not be substituted for each other

- Renal function and QTc interval must be determined prior to initiation and monitored closely throughout therapy. Dosing adjustments should be made accordingly
- Electrolyte abnormalities (hypokalemia, hypomagnesemia) should be corrected prior to initiation
- Avoid use in patients with heart failure

ANTICHOLINERGICS, EMERGENCY

Introduction

Atropine is an anticholinergic agent used primarily intravenously for bradycardia during advanced cardiovascular life support (ACLS). It is also available in ophthalmic form to produce mydriasis. Many other anticholinergic medications exist that are used for noncardiac indications, ranging from pulmonary diseases to incontinence. Those are discussed elsewhere.

Mechanism of Action for the Drug Class

Atropine competitively blocks the action of acetylcholine on all muscarinic receptors. Anticholinergic activity in smooth muscle, secretory glands, and CNS results in tachycardia, dried secretions, and bronchodilation.

◉ Atropine

Brand Names

AtroPen, Atropine Care, Isopto Atropine

Generic Name

Atropine

Rx Only

Dosage Forms

Injection, ophthalmic ointment, and solution

Usage

Antidote for mushroom poisoning, *bradycardia/heart block,* cycloplegic refraction, *mydriasis induction,* organophosphate poisoning, poisoning by parasympathomimetic drug, premedication for anesthetic procedure, uveitis

Pregnancy Category B/C (manufacturer specific)

Dosing

- Bradycardia: 0.5 mg IV, repeat every 3 to 5 minutes up to 3 mg
- Poisoning: Dosing depends on poison
- Preanesthesia: 0.4–0.6 mg IV, IM, or SUB-Q; repeat every 4–6 hours as needed to inhibit salivation/secretions

Adverse Reactions: Most Common

Flushing, tachycardia

Adverse Reactions: Rare/Severe/Important

Acute organic brain syndrome (confusion, delirium, restlessness, somnolence, psychosis), anhidrosis, arrhythmias, paralytic ileus, urinary retention

Major Drug Interactions

None

Contraindications

Narrow-angle glaucoma (ophthalmic), pyloric stenosis

Essential Monitoring Parameters

Blood pressure, heart rate, mental status

Key Points

- Atropine is a potent anticholinergic agent used primarily in the management of bradycardia/heart block
- Ophthalmic formulations are also commonly used to produce mydriasis

ANTIDIURETIC HORMONE

Introduction

Vasopressin has multiple mechanisms and is primarily used to increase blood pressure in patients with hypotension/septic shock. It can replace other pressor agents in some patients.

Mechanism of Action for the Drug Class

Vasopressin acts on vasopressin receptors V_1 and V_2. Stimulation of the V_2 receptor is greater than V_1 and causes increased water permeability in the renal tubule, resulting in decreased urine volume. In addition, vasopressin is a

direct vasoconstrictor and increases blood vessel response to catecholamines and acts on portal blood pressure to restrict blood flow to esophageal varices.

Vasopressin

Brand Name
Pitressin, Vasostrict

Generic Name
Vasopressin

Rx Only

Dosage Form
Injection

Usage
Shock/hypotension, diabetes insipidus, esophageal varices, GI hemorrhage

Pregnancy Category C

Dosing
- Diabetes insipidus: 5–10 units IM/SUB-Q 2 to 4 times daily as needed
- Variceal hemorrhage: 0.2–0.4 units/min continuous infusion (doses up to 0.8 units/min have been used)
- Shock/hypotension: 0.01–0.04 units/min

Adverse Reactions: Most Common
Headache, abdominal cramps, nausea, vomiting, tremor

Adverse Reactions: Rare/Severe/Important
Heart failure, decreased cardiac output, limb/skin necrosis, myocardial infarction

Major Drug Interactions
Drugs Affecting Vasopressin
- Vasodilators: Decrease efficacy
- IV drugs: Check for compatibility when infusing through same line

Essential Monitoring Parameters
Serum and urine sodium, blood pressure, heart rate, cardiac output/cardiac index, ECG

Key Point
Close hemodynamic monitoring and titration of dose is necessary

BETA BLOCKERS

Introduction
Beta-adrenergic antagonists, commonly called beta blockers, are one of the most widely used cardiovascular medications. They have multiple clinical effects and are very effective at preventing morbidity and mortality for several disease states, although they can be sedating to patients.

Mechanism of Action for the Drug Class
Beta blockers competitively block response to beta-adrenergic stimulation at the receptor level, which results in decreases in heart rate, myocardial contractility, blood pressure, and myocardial oxygen demand. Beta-1 selective agents selectively block beta-1 receptors with little to no effect on beta-2 receptors, whereas nonselective agents antagonize both types. Some nonselective agents have alpha-adrenergic blocking activity, which results in further decreases in blood pressure. Additionally, some agents have intrinsic sympathomimetic activity (partial beta agonist activity), which results in smaller decreases in heart rate and contractility compared with other beta blockers.

Members of the Drug Class
In this section: Atenolol, carvedilol, labetalol, metoprolol, nebivolol, propranolol

Others: Acebutolol, betaxolol, bisoprolol, esmolol, nadolol, penbutolol, pindolol, sotalol, timolol

Rx Only for the Drug Class

Usage for the Drug Class
- Cardiovascular uses: *Angina, arrhythmias, HFrEF* (bisoprolol, carvedilol, and metoprolol XL only), hypertension, *myocardial infarction,* premature ventricular contractions, adjunctive management of pheochromocytoma
- Noncardiovascular uses: Essential tremors, migraine prophylaxis, adjunctive therapy in the treatment of Parkinson disease, aggressive behavior, treatment of antipsychotic-induced akathisia, variceal hemorrhage prophylaxis, treatment of performance anxiety, adjunctive treatment in schizophrenia and acute panic and treatment of thyrotoxicosis symptoms

Adverse Reactions for the Drug Class: Most Common
Bradycardia, decreased sexual ability, dizziness, hypotension, fatigue, lethargy

Adverse Reactions for the Drug Class: Rare/Severe/Important
Heart block, worsening heart failure symptoms, bronchoconstriction (nonselective or selective at higher

doses), exacerbations of peripheral vascular disease and Raynaud's disease, depression

Major Drug Interactions for the Drug Class

Drugs Affecting Beta Blockers

Amiodarone, clonidine, digoxin, diltiazem, dronedarone, verapamil: Enhance AV nodal inhibition

Beta Blocker Effects on Other Drugs

Oral antidiabetic agents, insulin: May mask the symptoms of hypoglycemia

Contraindications for the Drug Class

Sinus bradycardia, sinus node dysfunction, cardiogenic shock, second- or third-degree heart block (except in patients with a pacemaker)

Essential Monitoring Parameters for the Drug Class

Heart rate, blood pressure

Counseling Points for the Drug Class

- Do not abruptly stop taking medication. Beta blockers should be gradually tapered when stopping to avoid tachycardia, hypertension, and/or ischemia.
- May increase blood glucose. They may also mask the symptoms of hypoglycemia.
- May decrease heart rate and blood pressure. Tell your healthcare provider if you experience any dizziness or lightheadedness.

Key Points for the Drug Class

- **Black Box Warning:**
  - Abrupt withdrawal: Beta blockers should not be withdrawn abruptly (particularly in patients with coronary artery disease), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia
- Beta blockers are one of the most widely used cardiovascular agents because they are very effective for the treatment of many cardiovascular diseases. They are also used for some off-label uses not associated directly with cardiovascular disease.
- Bisoprolol, carvedilol, and metoprolol succinate have been shown to reduce morbidity and mortality in patients with HFrEF and should be used preferentially over other beta blockers in those patients
- When used in patients with heart failure, those medications should be initiated only in stable patients or hospitalized patients after volume status has been optimized
- Nonselective beta blockers should be avoided in patients with asthma because they can lead to asthma exacerbations. Selective agents should be used cautiously.

◉ Atenolol (beta-1 selective)

Brand Name

Tenormin

Generic Name

Atenolol (beta-1 selective)

Dosage Form

Tablet

Pregnancy Category D

Dosing

- 25–100 mg once or twice daily (maximum 200 mg/day)
- Use lower doses in elderly and in patients with renal dysfunction due to significantly increased half-life
- Renal dosage adjustment:
  - CrCl 15–35 ml/min: Maximum dose of 50 mg daily
  - CrCl < 15 ml/min: Maximum dose 25 mg daily

◉ Carvedilol (nonselective with alpha-1 blockade)

Brand Names

Coreg, Coreg CR

Generic Name

Carvedilol (nonselective with alpha-1 blockade)

Dosage Forms

Tablet, extended-release capsule

Pregnancy Category C

Dosing

- Immediate release: 3.125–50 mg twice daily
- Heart failure: initiate only in stable patients or hospitalized patients after volume status has been optimized at 3.125 mg twice daily, then titrate dose as tolerated to a target dose of 25 mg twice daily (or 50 mg twice daily if > 85 kg)
- Extended release: 10–80 mg once daily
- Hepatic dose adjustment:
  - Mild to moderate impairment: There are no dosage adjustments provided in the manufacturer's labeling.
  - Severe impairment: Use is contraindicated

Counseling Point

Take with food to minimize the risk of orthostatic hypotension

Key Points

- Recommended for patients with HFrEF to reduce morbidity and mortality
- Conversion from immediate-release to extended-release is not 1:1
- Inhibits alpha-1 receptors as well, unlike most other beta blockers, which provides added blood pressure lowering

◉ Labetalol (nonselective with alpha-1 blockade)

Brand Names

Trandate (no longer available), Normodyne (no longer available)

Generic Name

Labetalol (nonselective with alpha-1 blockade)

Dosage Forms

Tablet, injection

Pregnancy Category C

Dosing

- Oral: 100 mg twice daily, can be given up to 2400 mg daily in divided doses
- IV:
  - Repeat boluses: 20–80 mg slow IV push every 10 minutes up to total 300 mg until response
  - Continuous infusion: 0.5–2 mg/min up to 300 mg total cumulative dose. In rare instances, when clinically necessary (i.e., BP lowering in aortic dissection or acute ischemic stroke), continuous infusions up to 8 mg/minute can be utilized. Due to the prolonged duration of action, careful monitoring should be extended for the duration of the infusion and for several hours after the infusion. Excessive administration may result in prolonged hypotension and/or bradycardia.
- IV to oral conversion: Upon discontinuation of IV infusion, may initiate oral dose of 200 mg followed in 6 to 12 hours with an additional dose of 200–400 mg. Thereafter, dose patients with 400 to 2400 mg/day in divided doses, depending on blood pressure response.

Key Points

- Often used for hypertension and hypertensive emergencies, in part, due to the availability of an IV form
- Labetalol is considered a drug of choice in patients presenting with hypertensive emergencies in the setting of ischemic stroke and subarachnoid hemorrhage
- Labetalol is a preferred agent in the treatment of hypertension in pregnant patients, despite its pregnancy category C status
- Inhibits alpha-1 receptors as well, unlike most other beta blockers; however, the ratios of alpha- to beta blockade differ, depending on the route of administration: 1:3 (oral) and 1:7 (IV).

◉ Metoprolol (beta-1 selective)

Brand Names

Lopressor (metoprolol tartrate), Toprol XL (metoprolol succinate)

Generic Names

Metoprolol tartrate, metoprolol succinate (beta-1 selective)

Dosage Forms

Tablet (as tartrate), extended release tablet (as succinate), injection (as tartrate)

Pregnancy Category C

Dosing

- Oral, immediate release: 12.5–50 mg every 6 to 12 hours, titrated up to 400 mg/day in divided doses (duration of action is dose-dependent—smaller doses may require more frequent dosing)
- Oral, extended release: 25–50 mg once daily, titrate up to 400 mg once daily
- Heart failure: initiate only in stable patients or hospitalized patients after volume status has been optimized 12.5–25 mg once daily, then titrate dose as tolerated to a target dose of 200 mg/day
- IV: 1.25–5 mg every 6 to 12 hours, titrate up to 15 mg every 3 to 6 hours
- When switching from immediate release (metoprolol tartrate) to extended release (metoprolol succinate), the same total daily dose of metoprolol should be used
- When switching between oral and intravenous dosage forms, in most cases, equivalent beta-blocking effect is achieved with a 2.5:1 (Oral:IV) dosing ratio; however, some evidence suggests a range of 2:1 to 5:1 (Oral:IV) for the dosing ratio

Key Points

- Only the extended-release formulation (metoprolol succinate) is recommended for use in patients with HFrEF to reduce mortality
- When switching from immediate release (metoprolol tartrate) to extended release (metoprolol succinate), the same total daily dose of metoprolol should be used
- When switching between oral and intravenous dosage forms, in most cases, equivalent beta-blocking effect is achieved with a 2.5:1 (Oral:IV) dosing ratio

◉ Propranolol (nonselective)

Brand Names

Hemangeol, Inderal LA, Inderal XL, InnoPran XL

Generic Name

Propranolol (nonselective)

Dosage Forms

Tablet, extended-release capsule, oral solution, injection

Dosing

- Oral: 10–40 mg every 6 to 12 hours, titrated up to 640 mg/day in 2 to 4 divided doses (once daily, if long-acting formulation)

- IV: 1–3 mg every 2 to 5 minutes up to 5 mg; may administer by rapid infusion at a rate of 1 mg/minute or by slow infusion over 30 minutes

Key Points

- Propranolol is the beta blocker of choice for treatment of thyroid storm because it is thought to block conversion of T_4 to T_3 at higher doses
- Propranolol is also used for the treatment of performance anxiety and migraine prophylaxis, although other beta blockers also are used

CALCIUM CHANNEL BLOCKERS, BENZOTHIAZEPINES

Introduction

Diltiazem is the only member of the benzothiazepine class of calcium channel blockers. It is commonly used for the treatment of hypertension and heart rate control in patients with atrial fibrillation due to its effects on both blood pressure and cardiac conduction.

Mechanism of Action

Diltiazem inhibits the movement of calcium ions across the cell membranes. The effects on the cardiovascular system include relaxation of coronary vascular smooth muscle and coronary vasodilation. It also increases myocardial oxygen delivery and depresses both impulse formation and conduction velocity in the atrioventricular node.

⦿ Diltiazem

Brand Names

Cardizem, Cardizem CD, Cardizem LA, Cartia XT, Dilt-XR, DilTIAZem CD, Matzim LA, Taztia XT, Tiazac

Generic Name

Diltiazem

Rx Only

Dosage Forms

Tablet, extended-release tablet, extended-release capsule, injection

Usage

Angina, atrial arrhythmias, hypertension, proteinuria, supraventricular tachycardias

Pregnancy Category C

Dosing

- PO: 120–540 mg/day (in one to four divided doses, depending on the drug formulation)
- IV:
  - Bolus: 10–25 mg (0.25 mg/kg actual body weight) given over 2 minutes
  - Continuous infusion: 5–15 mg/hour (infusions > 24 hours or infusion rates > 15 mg/hour are not recommended)
  - IV to PO conversion: Oral dose = [IV rate (mg/hour) × 3 + 3] × 10

Adverse Reactions: Most Common

Bradycardia, dizziness, lightheadedness, flushing, headache, hypotension, peripheral edema

Adverse Reactions: Rare/Severe/Important

Third-degree AV block, decreased heart contractility (worsening symptoms of heart failure), dermatologic reactions (e.g., SJS, TEN), gingival hyperplasia

Major Drug Interactions

Drugs Affecting Diltiazem

- CYP3A4 inhibitors: Increase effects
- Azole antifungal agents: Increase hypotensive effect
- Carbamazepine: Decreases hypotensive effect
- Clarithromycin, erythromycin: Decrease metabolism
- Rifampin: Decreases hypotensive effect
- Sildenafil: Increases hypotensive effect

Diltiazem's Effect on Other Drugs

- Antihypertensive medications: Additive hypotensive effects
- Amiodarone, beta blockers, and digoxin: Enhanced decrease in AV node conduction, increased risk of bradycardia
- Drugs metabolized by CYP3A4 (cyclosporine, HMG-CoA reductase inhibitors, tacrolimus): Increase concentrations
- Phenytoin: Decreases metabolism

Contraindications

Atrial fibrillation/flutter with an accessory bypass tract (e.g. Wolff-Parkinson-White syndrome, short PR syndrome), cardiogenic shock/heart failure, second- or

third-degree heart block (except in patients with a pacemaker), sick sinus syndrome (except in patients with a pacemaker), ventricular tachycardia (with wide-complex tachycardia [QRS ≥ 0.12 seconds])

Essential Monitoring Parameters

Heart rate, blood pressure, intravenous administration requires continuous ECG and blood pressure monitoring

Counseling Points

- Take on an empty stomach, if possible
- Do not crush long-acting formulations
- Capsules may be opened and the contents sprinkled on applesauce, which can be swallowed without chewing

Key Points

- Diltiazem is used for the treatment of hypertension, angina, and atrial fibrillation
- It should be avoided in patients with myocardial infarction and/or HFrEF because it is a negative inotrope
- Extended-release formulations are either daily or twice-daily dosing. Check with specific manufacturer recommendations.

CALCIUM CHANNEL BLOCKERS, DIHYDROPYRIDINES

Introduction

The dihydropyridine calcium channel blockers are widely used for the treatment of hypertension. They do not affect heart rate or contractility to the same extent as diltiazem and verapamil.

Mechanism of Action for the Drug Class

Those drugs inhibit movement of calcium ions across the cell membranes. The effects on the cardiovascular system include relaxation of coronary vascular smooth muscle and coronary vasodilation. They also increase myocardial oxygen supply. Some agents also act directly on vascular smooth muscle to produce peripheral arterial vasodilation, reducing peripheral vascular resistance and blood pressure.

Rx Only for the Drug Class

Usage for the Drug Class

Chronic stable angina, hypertension, proteinuria, pulmonary hypertension, Raynaud's disease, vasospastic angina

Pregnancy Category C for the Drug Class

Adverse Reactions for the Drug Class: Most Common

Dizziness/lightheadedness, flushing, headache, hypotension, peripheral edema

Adverse Reactions for the Drug Class: Rare/Severe/Important

Orthostasis

Major Drug Interactions for the Drug Class

Drugs Affecting Dihydropyridines

- CYP3A4 inhibitors: Increase effects
- Carbamazepine: Decreases hypotensive effect
- Sildenafil: Increases hypotensive effect
- Azole antifungal agents: Increase hypotensive effects
- Rifampin: Decreases hypotensive effect

Dihydropyridines' Effects on Other Drugs

- Antihypertensive agents: Additive hypotension
- Simvastatin, tacrolimus: Increase effects/toxicity

Essential Monitoring Parameters for the Drug Class

Blood pressure, heart rate, peripheral edema

Counseling Points for the Drug Class

- Those medications can be taken without regard to meals
- Do not stop therapy abruptly

Key Points for the Drug Class

- The dihydropyridine calcium channel blockers are used primarily for the treatment of hypertension. They also have a role in the treatment of chronic stable angina.
- Immediate-release formulations of nifedipine are no longer recommended due to increased mortality compared with extended-release formulations, although both forms are still available
- Use with extreme caution in patients with severe aortic stenosis; may reduce coronary perfusion, resulting in ischemia

Members of the Drug Class

In this section: Amlodipine, felodipine, nifedipine
Others: Clevidipine, isradipine, nicardipine, nimodipine, nisoldipine

◉ Amlodipine

Brand Name

Norvasc

Generic Name

Amlodipine

Dosage Form

Tablet

Dosing

- 2.5–10 mg daily (peak antihypertensive effect is delayed due to long half-life; dosage titration should occur after 7 to 14 days on a given dose)
- Hepatic dose adjustments:
  - Initial dose: 2.5-5 mg/day, titrate more slowly in patients with severe hepatic impairment

Key Points

- Amlodipine has a long half-life and, therefore, can be dosed once daily
- It is not an extended-release formulation and, therefore, can be crushed
- Peak antihypertensive effect is delayed due to long half-life; dosage titration should occur after 7 to 14 days on a given dose
- Peripheral edema is a dose-dependent side effect and more common in females and patients with heart failure

Felodipine

Brand Name

Plendil (no longer available)

Generic Name

Felodipine

Dosage Form

Extended-release tablet

Dosing

- 2.5–20 mg daily
- Doses >10 mg daily are associated with greater antihypertensive effects but also a large increase in the incidence of peripheral edema and other vasodilatory adverse effects

Nifedipine

Brand Names

Adalat CC, Procardia, Procardia XL

Generic Name

Nifedipine

Dosage Forms

Capsule, extended-release tablet

Dosing

30–180 mg/day (in three doses or once daily, depending on the formulation)

Key Points

- The immediate-release formulation is not recommended for use. Serious adverse events (e.g., death, cerebrovascular ischemia, syncope, stroke, acute myocardial infarction, and fetal distress) have been reported. Considered contraindicated in patients with ST-elevation myocardial infarction.
- Extended-release formulations contain a nondeformable matrix, which is expelled in stool. Use caution in patients with a known stricture/narrowing of the GI tract.
- Nifedipine has negative inotropic effects and may worsen heart failure symptoms

CALCIUM CHANNEL BLOCKERS, PHENYLALKYLAMINES

Introduction

Verapamil is the only available member of the phenylalkylamine class of calcium channel blockers. It is used for the treatment of hypertension and heart rate control in patients with atrial fibrillation.

Mechanism of Action

Verapamil inhibits the movement of calcium ions across the cell membranes. The effects on the cardiovascular system include relaxation of coronary vascular smooth muscle, coronary vasodilation, and decreased myocardial contractility. It also increases myocardial oxygen delivery and depresses both impulse formation and conduction velocity in the atrioventricular node.

Verapamil

Brand Names

Calan, Calan SR, Verelan, Verelan PM

Generic Name

Verapamil

Rx Only

Dosage Forms

Tablet, extended-release tablet, sustained-release tablet, extended-release capsule, injection

Usage

- Cardiovascular uses: *Angina, atrial fibrillation and flutter,* hypertension, supraventricular tachycardia
- Noncardiovascular uses: Manic manifestations of bipolar disorder, migraine prophylaxis

Pregnancy Category C

Dosing

- Oral: 120–480 mg/day (given daily or in divided doses, depending on the formulation)
- IV:
  - Bolus: 0.075 to 0.15 mg/kg (usual dose: 5–10 mg) over at least 2 minutes; if no response, may give an additional 10 mg bolus after 15 to 30 minutes; if patient responds to the initial or repeat bolus dose, may begin a continuous infusion
  - Continuous infusion: 5 mg/hour; titrate to heart rate goal
- Renal dosage adjustment: If CrCl < 10 ml/min, administer 50% to 75% of normal dose
- Hepatic dosage adjustment: In cirrhosis, reduce dose to 20% of normal and monitor ECG

Adverse Reactions: Most Common

Bradycardia, constipation (7–12%), dizziness/lightheadedness, gingival hyperplasia, headache, hypotension, peripheral edema

Adverse Reactions: Rare/Severe/Important

Worsening of heart failure, increased hepatic enzymes

Major Drug Interactions

Drugs Affecting Verapamil

- Amiodarone, beta blockers: Increase risk of bradycardia
- Carbamazepine: Decreases hypotensive effect
- Clarithromycin, erythromycin: Increase levels
- Fluconazole, itraconazole: Increase effects

Verapamil's Effect on Other Drugs

- Digoxin: Increases levels
- Dofetilide: Increases levels, leading to ventricular arrhythmias (contraindicated)
- Cyclosporine, tacrolimus: Increase levels
- Phenytoin: Decreases metabolism
- Theophylline: Increases levels
- Lovastatin, simvastatin, atorvastatin: Increase levels/toxicity

Contraindications

Severe left ventricular dysfunction/cardiogenic shock/heart failure, sick sinus syndrome or second- or third-degree AV block (except in patients with a ventricular pacemaker), atrial fibrillation/flutter with an accessory bypass tract (e.g., Wolff-Parkinson-White syndrome, Lown-Ganong-Levine syndrome), concurrent use with dofetilide

Essential Monitoring Parameters

Blood pressure, heart rate, constipation, periodic liver function tests

Counseling Points

- Take sustained-release tablets with food or milk; other formulations may be taken without regard to food
- Sprinkling contents of capsules onto food does not affect absorption
- Do not crush or chew extended- or sustained-release products

Key Points

- Verapamil is used for the treatment of hypertension and atrial fibrillation
- It should be avoided in patients with acute myocardial infarction and/or HFrEF because it is a negative inotrope
- Patients must be counseled on the side effects, particularly constipation
- Dosing intervals vary based on the product

LOOP DIURETICS

Introduction

The loop diuretics are very effective at reducing pulmonary and peripheral edema in patients who are volume overloaded. They are used to treat symptoms of congestion in patients with heart failure and other diseases that cause fluid retention/overload. They have been supplanted by more effective agents in the treatment of hypertension.

Mechanism of Action for the Drug Class

Loop diuretics are named as such because they primarily inhibit the reabsorption of sodium and chloride at the thick ascending limb of the loop of Henle, increasing the excretion of sodium, water, chloride, calcium, and magnesium

Members of the Drug Class

In this section: Furosemide
Others: Bumetanide, ethacrynic acid, torsemide

◉ Furosemide

Brand Name

Lasix

Generic Name
Furosemide

Rx Only

Dosage Forms
Tablet, oral solution, injection

Usage
Edema, hypertension, ascites due to cirrhosis

Pregnancy Category C

Dosing
- Oral:
  - Initial dose: 20–40 mg once or twice daily
  - Dosage adjustment: Up to 600 mg per day in 2 to 4 divided doses
- IV:
  - IV bolus: Doses of 10–200 mg administered every 6–12 hours or as needed
  - Continuous infusion: 10–40 mg/hour
  - Oral bioavailability is poor; therefore, equivalent IV dose is 50% of PO dose

Adverse Reactions: Most Common
Dehydration, electrolyte depletion, hyperuricemia, hypochloremic alkalosis, hypotension, orthostasis

Adverse Reactions: Rare/Severe/Important
Renal function impairment, ototoxicity (increased risk with higher doses and rapid IV administration), skin rash

Major Drug Interactions
Drugs Affecting Furosemide
- NSAIDs: Decrease diuresis

Furosemide's Effects on Other Drugs
- Aminoglycosides: Increase ototoxicity
- Lithium: Increases levels
- Digoxin: Increases risk of toxicity due to furosemide-induced hypokalemia

Contraindications
Sulfonamide ("sulfa") allergy (note: cross-reactivity between antibiotic sulfonamides and nonantibiotic sulfonamides may actually not occur or, at the very least, this potential is extremely low)

Essential Monitoring Parameters
Blood pressure, renal function (serum creatinine, urine output), electrolytes (K, Mg), ins and outs and weights (in patients with heart failure)

Counseling Points
- Avoid taking before bedtime to avoid having to urinate throughout the night
- Take with food or milk to reduce GI irritation
- With the possibility of hypokalemia, there may be a need for additional potassium in the diet or supplements; do not change your diet without first checking with your healthcare provider.
- Use caution when getting up suddenly from a lying or sitting position.
- Be cautious in using alcohol, while standing for long periods or exercising and during hot weather because of enhanced orthostatic hypotensive effects
- Regular monitoring of laboratory tests (potassium, serum creatinine), blood pressure, and body weight is necessary to ensure safe use of the drug and avoid adverse effects.

Key Points
- **Black Box Warning:**
  - Fluid/electrolyte loss: If given in excessive amounts, furosemide, similar to other loop diuretics, can lead to profound diuresis, resulting in fluid and electrolyte depletion
- Furosemide is commonly used to treat edema/fluid overload in patients with heart failure
- Furosemide is the most commonly used loop diuretic, but sometimes, concerns regarding oral bioavailability necessitate use of other loop diuretics
- Approximate dose equivalency for patients with normal renal function: Furosemide 40 mg PO = Furosemide 20 mg IV = bumetanide 1 mg IV/PO = torsemide 20 mg IV/PO = ethacrynic acid 50 mg IV/PO
- Cross-reactivity between antibiotic sulfonamides and nonantibiotic sulfonamides is extremely low; however, ethacrynic acid is the drug of choice in patients with a true allergy to loop diuretics because it does not contain a sulfonamide substituent.

NITRATES

Introduction
The nitrates are used for the treatment of angina, both unstable and chronic stable types. They are available in several formulations and dosage forms that differ in their onset and duration of action.

Mechanism of Action for the Drug Class
Nitrates relax vascular smooth muscle by stimulating intracellular cyclic guanosine monophosphate production. They cause predominantly venous dilation with some dose-dependent arterial effects.

Members of the Drug Class

In this section: Isosorbide mononitrate, nitroglycerin (sublingual)
Others: Isosorbide dinitrate, nitroglycerin (capsules, injection, topical ointment, transdermal patch, translingual spray)

Rx Only for the Drug Class

Usage for the Drug Class

- Cardiovascular uses: *Angina, heart failure,* hypertension, pulmonary hypertension
- Noncardiovascular uses: Esophageal spastic disorders, anal fissure (topical)

Adverse Reactions for the Drug Class: Most Common

Bradycardia, headache, hypotension, lightheadedness, syncope, weakness

Major Drug Interactions for the Drug Class

Drugs Affecting Nitrates

- Alcohol: Can cause severe hypotension and syncope
- Calcium channel blockers: May increase orthostatic hypotension
- Avanafil, sildenafil, tadalafil, vardenafil: Increase hypotensive effects (avoid use within 24 or 48 hours of each other; interval dependent on phosphodiesterase inhibitor)

Nitrates' Effects on Other Drugs

- Antihypertensive agents: Additive hypotension
- Ergot derivatives: Increase effects

Contraindications for the Drug Class

Systolic BP < 90 mm Hg, heart rate < 50 bpm, acute right ventricular infarction, concurrent use with phosphodiesterase inhibitors (avanafil, sildenafil, tadalafil, vardenafil, or avanafil), concurrent use with riociguat

Essential Monitoring Parameters for the Drug Class

Blood pressure, heart rate, headache

Counseling Points for the Drug Class

- Extended-release tablets and capsules: Do not crush or chew. Administer doses so that there is a "nitrate-free interval" of 10 to 12 hours.
- Sublingual tablets: Place under tongue or between cheek and gum. Rest during administration, preferably seated. Do not swallow tablets. Should feel a slight burning sensation under the tongue, which means the drug is working. Do not remove tablets from original glass container.
- Transdermal patch: Apply once daily to skin site that is free of hair and not subject to excessive movement. Avoid areas with cuts or irritations. Do not apply to distal parts of the extremities. Use caution when discarding to keep out of the reach of children or pets. Remove at night for a 12-hour "nitrate-free interval." May contain metal; remove prior to MRI.
- Headaches may occur and are a sign that the medication is working. Do not alter dosage schedule; aspirin or acetaminophen may be used to relieve pain.

Key Points for the Drug Class

- Nitrates are the drug of choice for quick relief of angina symptoms
- They are also used for long-term prevention of angina symptoms. However, they are not recommended as first-line treatment in patients with recent myocardial infarction (beta blockers are preferred).

◉ Isosorbide Mononitrate

Brand Names

Imdur (no longer available)

Generic Name

Isosorbide mononitrate

Dosage Forms

Tablet, extended-release tablet

Pregnancy Category B

Dosing

- Immediate release: 20 mg twice daily with the 2 doses given 7 hours apart (e.g., 8 AM and 3 PM) to decrease tolerance development
- Extended release: 30–120 mg once daily (rarely, 240 mg once daily may be required)

Key Point

Used for long-term treatment of chronic angina

◉ Nitroglycerin (sublingual)

Brand Name

Nitrostat

Generic Name

Nitroglycerin (sublingual)

Dosage Form

Sublingual tablet

Pregnancy Category C

Dosing

- 0.3–0.6 mg every 5 minutes up to 3 doses as needed for relief of anginal attack. If pain is unrelieved or worsened 3 to 5 minutes after 1 dose, the patient or caregiver should call 9-1-1 immediately.
- May use prophylactically 5 to 10 minutes before activities that precipitate an attack

Key Points

- Sublingual tablets are used for the relief of angina attacks only. They are not used for long-term treatment of angina.
- Sublingual tablets must be stored in original containers away from humidity and moisture
- Patients should not crush sublingual tablets; they should just place under tongue and allow to dissolve

PHOSPHODIESTERASE ENZYME INHIBITORS, INOTROPES

Introduction

The phosphodiesterase inhibitor milrinone is a positive inotrope used in the treatment of decompensated heart failure. In addition to being a positive inotrope, it results in significant decreases in blood pressure.

Mechanism of Action for the Drug Class

Inhibition of the enzyme cAMP phosphodiesterase results in increased cAMP in cardiac and vascular muscle. Increased cAMP increases intracellular calcium, thereby increasing contractility in cardiac muscle (positive inotrope) and relaxation in vasculature (vasodilation).

Rx Only for the Drug Class

◉ Milrinone

Brand Name

Primacor (no longer available)

Generic Name

Milrinone

Dosage Forms

Injection

Usage

Acute decompensated heart failure, palliation of symptoms/bridge therapy in end-stage heart failure

Pregnancy Category C

Dosing

- Loading dose is optional (50 µg/kg IVPB), but not recommended by ACCF/AHA 2013 heart failure guidelines
- Maintenance dose: 0.1 to 0.75 µg/kg/minute
- Renal dosage adjustments: Half-life is increased, consider starting at lower end of dosing range and titrating more slowly

Adverse Reactions: Most Common

Arrhythmias, hypotension

Adverse Reactions: Rare/Severe/Important

Ventricular arrhythmias, thrombocytopenia

Major Drug Interactions

Drugs Affecting Milrinone

Negative inotropes: Decrease efficacy

Contraindication

Significant hypotension (use with caution)

Essential Monitoring Parameters

Cardiac output/cardiac index, pulmonary capillary wedge pressure, blood pressure, fluid status, ECG, electrolytes (potassium and magnesium), renal function

Key Points

- Milrinone is commonly used for the treatment of acute decompensated and end-stage heart failure
- It increases cardiac output and is a potent vasodilator. Blood pressure must be monitored closely
- Use is associated with increased risk of arrhythmias/mortality; therefore, the benefit must outweigh the risk
- Milrinone is the preferred inotrope (over dobutamine) for patients also receiving beta blockers

POTASSIUM-SPARING DIURETICS, ALDOSTERONE ANTAGONISTS, MINERALOCORTICOID RECEPTOR ANTAGONISTS

Introduction

The aldosterone antagonists/mineralocorticoid receptor antagonists can be used as diuretics; however, they are more commonly used as adjunctive therapy to reduce morbidity and mortality in patients with HFrEF NYHA class II-IV.

Mechanism of Action for the Drug Class

Aldosterone antagonists/mineralocorticoid receptor antagonists competitively inhibit aldosterone, which binds to mineralocorticoid receptors of the distal tubules in the kidney. This action increases the excretion of sodium chloride and water but not potassium and hydrogen ions. Mineralocorticoid receptor antagonists also block mineralocorticoid receptors located in the heart, blood vessels, and brain, which may prevent myocardial and vascular fibrosis. Spironolactone is nonselective and additionally binds to glucocorticoid, progesterone, and androgen receptors; whereas eplerenone selectively binds to mineralocorticoid receptors.

Members of the Drug Class

In this section: Spironolactone
Other: Eplerenone

Rx Only for the Drug Class

Spironolactone

Brand Name

Aldactone

Generic Name

Spironolactone

Dosage Form

Tablet

Usage

Edema or ascites in patients with cirrhosis of the liver, heart failure, hyperaldosteronism, hypertension, hypokalemia, acne in women, hirsutism

Pregnancy Category C

Dosing

- 25–200 mg/day in 1 to 2 divided doses, depending on indication
  - Heart failure: 12.5–25 mg daily; maximum 50 mg daily
- Renal dosage adjustment:
  - Heart failure: eGFR 30–49 ml/min/1.73 m^2: Initial dose: 12.5 mg once daily or every other day; maintenance dose (after 4 weeks of treatment with potassium ≤ 5 mEq/l): 12.5 to 25 mg once daily
  - Heart failure: eGFR <30 ml/min/1.73 m^2: Not recommended
  - Patients ≥ 65 years with CrCl < 30 ml/min (regardless of indication): Avoid use due to risk of hyperkalemia

Adverse Reactions: Most Common

Hyperkalemia, cramping, diarrhea

Adverse Reactions: Rare/Severe/Important

Gynecomastia, renal dysfunction

Major Drug Interactions

Drugs Affecting Spironolactone

Potassium supplements, NSAIDs: Increase risk of hyperkalemia

Spironolactone's Effects on Other Drugs

ACE inhibitors, ARBs, cyclosporine, tacrolimus, triamterene, trimethoprim: Increase risk of hyperkalemia

Contraindications

- Heart failure: Serum creatinine > 2 mg/dL in women or > 2.5 mg/dL in men
- Potassium > 5 mEq/L
- Patients with anuria, acute renal impairment, or significant impairment of renal excretory function

Essential Monitoring Parameters

Renal function (serum creatinine, urine output), potassium, blood pressure

Counseling Points

- Avoid ingestion of foods high in potassium or use of salt substitutes or other potassium supplements without the advice of your healthcare provider
- Instruct patients with heart failure to discontinue use during an episode of diarrhea or dehydration or when loop diuretic therapy is interrupted due to increased risk of hyperkalemia

Key Points

- **Black Box Warning:**
  - Tumorigenic: Shown to be tumorigenic in chronic toxicity animal studies. Avoid unnecessary use.
- Spironolactone is used as a diuretic in patients with cirrhosis of the liver. Use in those patients requires much higher dosing (up to 200 mg daily) than what is recommended in patients with heart failure (maximum 50 mg daily).
- The main role of spironolactone in patients with HFrEF is to reduce morbidity and mortality when used in combination with beta blockers and ACEIs or ARBs
- Eplerenone is the preferred agent in patients who develop intolerable gynecomastia
- Patients must be monitored closely for hyperkalemia and renal dysfunction because those could result in potentially fatal adverse effects (hyperkalemia-induced arrhythmias)

THIAZIDE DIURETICS

Introduction

Thiazide diuretics are recommended for first-line therapy in the treatment of hypertension. They can also be used in patients with edema, often in combination with a loop diuretic for synergistic effects since they do not result in as significant reductions in edema as loop diuretics on their own.

Mechanism of Action for the Drug Class

Inhibit reabsorption of sodium and chloride in the distal tubules, resulting in increased urinary excretion of sodium and chloride.

Members of the Drug Class

In this section: Hydrochlorothiazide
Others: Bendroflumethiazide, chlorothiazide, chlorthalidone, methyclothiazide

Hydrochlorothiazide

Brand Name
Microzide

Generic Name
Hydrochlorothiazide

Rx Only

Dosage Forms
Tablet, capsule

Usage
Cardiovascular uses: *hypertension,* edema

Pregnancy Category B

Dosing
- 12.5–50 mg daily
- Renal dosage adjustment:
  - Ineffective if CrCl < 30 ml/min (except in combination with loop diuretics)
  - CrCl < 10 ml/min: Use not recommended

Adverse Reactions: Most Common
Hypokalemia, orthostatic hypotension, stomach upset

Adverse Reactions: Rare/Severe/Important
Gout, hypercalcemia, hypercholesterolemia, hypochloremic alkalosis, ocular effects (acute transient myopia and acute angle-closure glaucoma), photosensitivity

Major Drug Interactions

Drugs Affecting Hydrochlorothiazide
- Loop diuretics: Enhance diuresis
- NSAIDs: May decrease efficacy of thiazides

Hydrochlorothiazide's Effect on Other Drugs
- Digoxin: Thiazide-induced hypokalemia may precipitate digitalis-induced arrhythmias
- Dofetilide: Increases levels, leading to ventricular arrhythmias **(contraindicated)**
- Lithium: Increases levels

Counseling Points
- Take in the morning to avoid increased urination at night
- Antihypertensive effects may take several days

Key Points
- The thiazide diuretics are recommended as first-line in the treatment of hypertension
- They can also be used for edema; however, they often only work for mild edema, and a loop diuretic is often required for more severe edema associated with heart failure
- The 50-mg dose of hydrochlorothiazide has increased adverse effects without added efficacy and should generally be avoided

VASODILATORS, HYDRALAZINE

Introduction
Hydralazine is used for the treatment of refractory hypertension and heart failure. It is often not used as first-line treatment because of its inconvenient dosing schedule and variable blood pressure response due to genetic variations between the ability of patients to acetylate the drug. It is sometimes used in heart failure in combination with nitrates in patients who do not respond to or are intolerant of ACEIs or ARBs or in African-American patients who are already receiving guideline-directed medical therapy.

Mechanism of Action for the Drug Class
Hydralazine causes direct vasodilation of arterioles (with little effect on veins), resulting in decreased systemic vascular resistance.

Hydralazine

Brand Name
Apresoline

Generic Name
Hydralazine

Rx Only

Dosage Forms
Tablet, injection

Usage
Hypertension, heart failure (in combination with nitrate therapy)

Pregnancy Category C

Dosing
- Oral: 10 mg 4 times daily for the first 2 to 4 days; increase to 25 mg 4 times daily for the balance of the first week; further increase to 50 mg 4 times daily (up to 300 mg daily may be required in resistant patients)
- HFrEF NYHA class III-IV (African-Americans): hydralazine 25–50 mg 3 or 4 times daily in combination with

isosorbide dinitrate 20–30 mg 3 or 4 times daily, titrated to hydralazine 300 mg/day in divided doses and isosorbide dinitrate 120 mg/day in divided doses; fixed-dose combination (BiDil): hydralazine 37.5 mg/isosorbide dinitrate 20 mg 3 times daily, titrated to hydralazine 75 mg/isosorbide dinitrate 40 mg 3 times daily
- IV: 10–20 mg every 4 to 6 hours as needed
- Renal dosage adjustment:
  - GFR > 10 ml/min: Administer every 8 hours
  - GFR < 10 ml/min: Administer every 8 to 16 hours

Adverse Reactions: Most Common
Angina, headache, nausea/vomiting, postural hypotension, tachycardia

Adverse Reactions: Rare/Severe/Important
Drug-induced, lupus-like syndrome (with higher doses), blood dyscrasias

Major Drug Interactions
None

Contraindications
Coronary artery disease (when used without a nitrate), mitral valve rheumatic heart disease

Essential Monitoring Parameters
Blood pressure (monitor closely with IV use), CBC periodically, heart rate

Counseling Points
- Hydralazine must be taken three to four times daily and taken consistently with regard to meals because food increases absorption
- Let your healthcare provider know if any lupus-like symptoms develop (e.g., fever, arthralgia, myalgia, malaise, pleuritic chest pain, edema, maculopapular facial rash)

Key Points
- Hydralazine is typically reserved for the treatment of refractory hypertension. It is also used for the treatment of heart failure in combination with nitrate therapy
- Duration of blood pressure effects may vary, depending on acetylator status (i.e., slow, intermediate, or rapid metabolism) of patient, which could result in either prolonged hypotension or a lack of therapeutic response
- Patient compliance may be an issue because it must be taken multiple times a day
- Hydralazine is a classic example of a drug that causes lupus-like syndrome. This adverse effect abates with discontinuation

VASODILATORS, NITROPRUSSIDE

Introduction
Nitroprusside is a short-acting, potent IV vasodilator used in hypertensive crises and acute decompensated heart failure. High doses and prolonged infusions are associated with increased toxicity, and close monitoring is necessary for safe use.

Mechanism of Action for the Drug Class
Nitroprusside acts on both venous and arterial smooth muscle, causing vasodilation, which leads to decreased preload and systemic vascular resistance, respectively.

◉ Nitroprusside

Brand Name
Nitropress

Generic Name
Nitroprusside

Rx Only

Dosage Form
Injection

Usage
Hypertensive emergency, acute decompensated heart failure, controlled hypotension to reduce bleeding during surgery

Pregnancy Category C

Dosing
- Initial dose: 0.1–0.2 μg/kg/minutes, titrate by 0.2–2 μg/kg/minutes every few minutes to achieve hemodynamic response to a maximum dose of 10 μg/kg/minutes (some experts recommend a maximum dose of 2 μg/kg/minutes)
- Hepatic/Renal dosage adjustments: > 3 μg/kg/minutes for > 72 hours increases risk of toxicity and should be avoided

Adverse Reactions: Most Common
Flushing, headache, nausea and vomiting

Adverse Reactions: Rare/Severe/Important
Cyanide and thiocyanate toxicity, increased intracranial pressure, methemoglobinemia, metabolic acidosis

Major Drug Interactions
IV drugs: Check for compatibility when infusing through same line

Contraindications

Treatment of compensatory hypertension (aortic coarctation, arteriovenous shunting), septic shock, congenital optic atrophy, or tobacco amblyopia

Use with extreme caution in patients with the following disease-related concerns: anemia, increased intracranial pressure, hypovolemia, myocardial infarction, renal and/or hepatic impairment.

Essential Monitoring Parameters

Blood pressure, heart rate (continuous cardiac monitoring is required during infusions), cyanide toxicity (increased risk with hepatic impairment), thiocyanate toxicity (increased risk with renal impairment), acid-base status

Key Points

- **Black Box Warning:**
  - Cyanide toxicity: Except when used briefly or at low (< 2 μg/kg/minute) infusion rates, nitroprusside gives rise to large cyanide quantities. Do not use the maximum dose for more than 10 minutes; if blood pressure is not controlled by the maximum rate (i.e., 10 μg/kg/minute) after 10 minutes, discontinue infusion. Monitor for cyanide toxicity via acid-base balance and venous oxygen concentration; however, clinicians should note that those indicators may not always reliably indicate cyanide toxicity.
  - Hypotension: Excessive hypotension, resulting in compromised perfusion of vital organs may occur; continuous blood pressure monitoring by experienced personnel is required
  - Appropriate administration: Solution must be further diluted with 5% dextrose in water. Do not administer by direct injection
- Nitroprusside is a very effective antihypertensive and vasodilator. Its fast onset and short half-life allow for immediate effects and close titration of dose.
- Severe toxicities are associated with increased dose and prolonged use. Therefore, transition to oral therapy should occur as soon as possible (avoid infusions > 72 hours).

COMBINATION DRUG THERAPIES

Introduction

The use of antihypertensive agents in combination is common. To decrease the pill burden and improve compliance, combination antihypertensive therapies combine two or three active drugs into one pill. Those formulations should not be used as initial therapy because they are not easy to titrate and should, therefore, only be used once it is known what doses of each medication a patient requires. Most combinations include a thiazide diuretic. Available combination products are summarized in **Table 5-2**.

Other Combination Products

Amlodipine/olmesartan, amlodipine/telmisartan, amlodipine/valsartan, clonidine/chlorthalidone

Multiple Combination Products

Amlodipine/olmesartan/hydrochlorothiazide, amlodipine/valsartan/hydrochlorothiazide

TABLE 5–2 Combination Antihypertensive Agents

Drug Class	Brand Name(s)	Generic Names	Other Similar Drugs
ACE inhibitor in combination with HCTZ	Zestoretic,	Lisinopril/HCTZ	Benazepril/HCTZ, captopril/HCTZ, cilazapril/HCTZ, enalapril/HCTZ, fosinopril/HCTZ, moexipril/HCTZ, quinapril/HCTZ, ramipril/HCTZ
ARB in combination with thiazide diuretic	Hyzaar	Losartan/HCTZ	Azilsartan/chlorthalidone, candesartan/HCTZ, eprosartan/HCTZ, irbesartan/HCTZ, olmesartan/HCTZ, telmisartan/HCTZ, valsartan/HCTZ
Dihydropyridine calcium channel blocker in combination with ACE inhibitor	Lotrel	Amlodipine/benazepril	None
Beta blockers in combination with thiazide diuretic	Ziac	Bisoprolol/HCTZ	Atenolol/chlorthalidone, nadolol/bendroflumethiazide, metoprolol/HCTZ, propranolol/HCTZ
Thiazide diuretic in combination with potassium-sparing diuretic	Dyazide, Maxzide, Maxzide-25	Triamterene/HCTZ	HCTZ/spironolactone, amiloride/HCTZ

REVIEW QUESTIONS

1. Which of the following is a common adverse reaction for alpha-1 adrenergic blockers?
   a. Hyperkalemia
   b. Intraoperative floppy iris syndrome
   c. Orthostatic hypotension
   d. Elevated serum creatinine

2. Which of the following statements regarding clonidine is incorrect?
   a. It is an alpha-2 receptor blocker
   b. Abrupt discontinuation of clonidine may result in rebound hypertension
   c. Overlapping of oral and transdermal clonidine may be necessary when initiating transdermal therapy
   d. Clonidine may cause CNS depression

3. Which of the following agents is a pure alpha-receptor agonist?
   a. Dobutamine
   b. Dopamine
   c. Milrinone
   d. Phenylephrine

4. Which of the following statements regarding dobutamine are *correct*?
   a. It is not recommended for severe decompensated heart failure
   b. It is a beta-1 and alpha-1 receptor agonist
   c. It is available as an oral formulation
   d. It should not be used with concomitant beta-blockers due to reduced effectiveness

5. Epinephrine stimulates which of the following receptors?
   a. Alpha-1
   b. Beta-1
   c. Beta-2
   d. All of the above

6. Which of the following are monitoring parameters for angiotensin receptor blockers (ARBs)?
   a. Angioedema
   b. Hyperkalemia
   c. Serum creatinine (renal function)
   d. All of the above

7. Which of the following is the preferred ARB for patients with heart failure?
   a. Bosentan
   b. Irbesartan
   c. Telmisartan
   d. Valsartan

8. Which of the following ACE inhibitors can be used for acute hypertension?
   a. Captopril
   b. Lisinopril
   c. Fosinopril
   d. Quinapril

9. Which of the following ACE inhibitors is available in an IV formulation?
   a. Enalaprilat
   b. Lisinopril
   c. Quinapril
   d. Fosinopril

10. Which of the following is a potentially dangerous adverse reaction to ranolazine?
    a. Torsades de pointes
    b. Acute renal failure
    c. Hyperkalemia
    d. Angioedema

11. Which of the following statements regarding ranolazine are *correct*?
    a. It is used for the treatment of chronic angina
    b. It increases blood pressure and heart rate
    c. It is contraindicated with diltiazem
    d. All of the above

12. Which of the following statements regarding amiodarone is *false*?
    a. It is a class II antiarrhythmic and it exhibits all four of the Vaughan–Williams antiarrhythmic medication classes
    b. Digoxin levels increase when given concomitantly with amiodarone
    c. Amiodarone usually requires a loading dose of 10 grams
    d. Patients should be monitored for hypothyroidism

13. Which of the following statements regarding digoxin is *false*?
    a. Digoxin levels should be drawn at least 6 hours following administration once the patient is at steady-state
    b. Digoxin drug levels for heart failure should be between 0.5–0.8 ng/dL
    c. Dosing should be adjusted for congestive heart failure status, renal function, and weight
    d. No dose adjustment is required when adding amiodarone to digoxin

14. Which of the following is the appropriate dose of sotalol in patients with a CrCl of 40–60 ml/min?

- **a.** 40 mg twice daily
- **b.** 80 mg daily
- **c.** 80 mg twice daily
- **d.** 160 mg twice daily

15. Sotalol is contraindicated in patients with a baseline QTc interval greater than:

- **a.** 300 msec
- **b.** 350 msec
- **c.** 400 msec
- **d.** 450 msec

16. Which of the following beta blockers blocks only beta-1 and beta-2 receptors?

- **a.** Atenolol
- **b.** Carvedilol
- **c.** Labetalol
- **d.** Propranolol

17. Which of the following beta blockers is recommended for patients with heart failure with reduced ejection fraction to reduce morbidity and mortality?

- **a.** Atenolol
- **b.** Bisoprolol
- **c.** Labetalol
- **d.** Metoprolol tartrate

18. Which of the following beta blockers should be avoided in patients with asthma?

- **a.** Propranolol
- **b.** Bisoprolol
- **c.** Metoprolol
- **d.** Atenolol

19. Which of the following antihypertensives are *not* used in hypertensive crises?

- **a.** Labetalol
- **b.** Hydralazine
- **c.** Nitroprusside
- **d.** Amlodipine

20. Which of the following dose *not* interact with amlodipine?

- **a.** Simvastatin
- **b.** Verapamil
- **c.** Acetaminophen
- **d.** Rifampin

21. Which of the following statements is *FALSE* regarding dihydropyridine calcium channel blockers?

- **a.** Immediate-release formulation of nifedipine is recommended
- **b.** Used for the treatment of hypertension
- **c.** Used for the treatment of angina
- **d.** Peripheral edema is a dose-dependent side effect

22. Verapamil belongs to which class of calcium channel blockers?

- **a.** Benzothiazepines
- **b.** Dihydropyridines
- **c.** Phenylalkylamines
- **d.** Verapamil is not a calcium channel blocker

23. Which of the following is *NOT* a contraindication with nondihydropyridine calcium channel blockers?

- **a.** Cardiogenic shock
- **b.** Third-degree AV block in a patient with a ventricular pacemaker
- **c.** Wolff-Parkinson-White syndrome
- **d.** Heart failure with reduced ejection fraction/left ventricular dysfunction

24. Which of the following is a loop diuretic?

- **a.** Chlorthalidone
- **b.** Spironolactone
- **c.** Bumetanide
- **d.** Metolazone

25. Which of the following is *NOT* a contraindication with nitrates?

- **a.** Systolic BP < 90 mmHg
- **b.** Heart rate < 50 bpm
- **c.** Concurrent use with phosphodiesterase inhibitors
- **d.** Concurrent use with hydralazine

26. What is a serious adverse effect of milrinone?

- **a.** Ventricular arrhythmias
- **b.** Hypertension
- **c.** Hyponatremia
- **d.** Constipation

27. What is a contraindication for spironolactone?

- **a.** Serum creatinine > 1.5 mg/dL in men
- **b.** Serum creatinine > 1.4 mg/dL in women
- **c.** Potassium > 4.5 mEq/L
- **d.** Anuria

28. At what CrCl is thiazide diuretic monotherapy considered to be ineffective?

- **a.** < 60 ml/min
- **b.** < 50 ml/min
- **c.** < 45 ml/min
- **d.** < 30 ml/min

29. Which of the following is not a monitoring parameter for nitroprusside?

- **a.** Blood pressure
- **b.** Respiratory rate
- **c.** Heart rate
- **d.** Acid-base status

30. Which is the most common medication that is used in combination antihypertensive products?

- **a.** Lisinopril
- **b.** Amlodipine
- **c.** Triamterene
- **d.** Hydrochlorothiazide

CHAPTER 6

Central Nervous System Agents

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5-HT RECEPTOR ANTAGONISTS

Introduction

Eletriptan, rizatriptan, and sumatriptan are selective agonists of vascular serotonin type 1–like receptors for the acute management of migraine headache with or without aura. Injectable sumatriptan is also indicated for the acute treatment of cluster headache. They are highly effective in many patients but must be avoided in those with concurrent cardiovascular disease. These agents should not be used for prophylaxis of migraine or cluster headache.

Mechanism of Action for the Drug Class

These drugs are 5-$HT_{1B/1D}$ receptor agonists at extracerebral and intracranial blood vessels, likely resulting in vasoconstriction and decreased trigeminal nerve transmission.

Members of the Drug Class

In this section: Eletriptan, rizatriptan, sumatriptan
Others: Almotriptan, frovatriptan, naratriptan, zolmitriptan

◉ Eletriptan

Brand Name

Relpax

Generic Name

Eletriptan

Rx Only

Dosage Form

Tablet

Usage

Acute treatment of migraine in adults, with or without aura

Pregnancy Category C

Dosing

- Initial dose: 20–40 mg; may repeat after 2 hours if headache returns
- Maximum single dose: 40 mg
- Maximum daily dose: 80 mg
- Renal dosage adjustment: No dosing adjustment needed; monitor for increased blood pressure
- Hepatic dosage adjustment:
  - Mild to moderate impairment: No adjustment needed
  - Severe impairment: Use is contraindicated

Adverse Reactions: Most Common

Nausea, asthenia, somnolence

Adverse Reactions: Rare/Severe/Important

Chest pain, coronary artery spasm, myocardial infarction, peripheral ischemia, transient myocardial ischemia, cerebrovascular accident, seizure

Major Drug Interactions

Drugs Affecting Eletriptan

- CYP3A4 inhibitors (fluconazole, ketoconazole, itraconazole, nefazodone, clarithromycin, ritonavir, nelfinavir): May increase peak plasma concentrations of eletriptan. Avoid administration of eletriptan within 72 hours of drugs with documented potent CYP3A4 inhibition.
- Ergot alkaloids (ergot, dihydroergotamine, methysergide) and other 5-HT_1 receptor agonists: Additive vasospastic effects. Use within 24 hours is contraindicated.
- Selective serotonin-reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs): Risk of serotonin syndrome
- Propranolol: Potential pharmacokinetic interaction (increases the maximum plasma concentrations of eletriptan); no dosage adjustment required

Contraindications

Known or suspected ischemic heart disease, coronary vasospasm (Prinzmetal variant angina), other serious underlying cardiovascular disease (uncontrolled hypertension), cerebrovascular syndromes, or peripheral vascular ischemia (ischemic bowel disease). Concomitant

use with another 5-HT$_1$ receptor agonist within 24 hours. Concomitant use with an ergot alkaloid within 24 hours. Basilar or hemiplegic migraine. Severe hepatic impairment (Child-Pugh grade C).

Counseling Points

- Take at first sign of migraine. This drug only treats migraine and will not prevent migraine headaches from occurring. Take exactly as directed; do not redose if no response is achieved.
- Take a second dose 2 or more hours after the first. Do not take more than 80 mg per day.
- Report chest pain, confusion, symptoms of a stroke, severe abdominal pain, shortness of breath, or neck/jaw problems since any of these could be signs of problems related to the drug. Do not take the drug again before seeing a healthcare provider.
- Do not take eletriptan within 24 hours of using an ergot alkaloid or another 5-HT$_1$ agonist

Key Points

- Eletriptan should be used only in patients with a clear diagnosis of migraine
- Be aware of important drug–drug interactions and serious cardiac effects

Rizatriptan

Brand Names

Maxalt, Maxalt MLT

Generic Name

Rizatriptan

Rx Only

Dosage Forms

Tablets, film-coated and orally disintegrating (MLT)

Usage

Acute treatment of migraine, with or without aura, in adults and children 6–17 years of age; tension-type headache in adults

Pregnancy Category C

Dosing

- Adults:
  - 5 or 10 mg, may repeat after 2 hours
  - Maximum dose: 30 mg/24 hour
- Children:
  - Safety and efficacy not established in pediatric patients < 6 years of age
  - 6–17 years, < 40 kg:
    - 5 mg
    - Maximum dose: 1 dose/24 hours
  - 6–17 years, ≥ 40 kg:
    - 10 mg
    - Maximum dose: 1 dose/24 hours
- Dosage adjustment with *concomitant propranolol:*
  - Adults: 5 mg; maximum is 3 doses in 24-hour period
  - Children ages 6–17 years, < 40 kg: Do not use
  - Children ages 6–17 years, ≥ 40 kg: 5 mg; maximum 1 dose/24 hours

Adverse Reactions: Most Common

Nausea, asthenia, dizziness, somnolence, fatigue

Adverse Reactions: Rare/Severe/Important

Chest pain, coronary artery spasm, hypertension, myocardial infarction, peripheral ischemia, ventricular arrhythmia, ischemic colitis, anaphylaxis, angioedema, analgesic overuse headache, cerebrovascular accident, serotonin syndrome

Major Drug Interactions

Drugs Affecting Rizatriptan

- Ergot alkaloids (ergotamine, dihydroergotamine, methysergide) and other 5-HT$_1$ receptor agonists: Additive vasospastic effects. Use within 24 hours is contraindicated.
- Monoamine oxidase inhibitors (MAOIs; phenelzine, selegiline, tranylcypromine): Potential pharmacokinetic interaction (increased systemic exposure to rizatriptan and active metabolite). Use of rizatriptan within 2 weeks of MAOI therapy is contraindicated.
- Propranolol: Potential pharmacokinetic interaction (increased plasma concentrations of rizatriptan). Maximum rizatriptan dosage of 5 mg per single dose and 3 doses per 24-hour period recommended.
- SSRIs and SNRIs: Risk of life-threatening serotonin syndrome. Observe patients carefully during treatment initiation, with dosage increases or when another serotonergic agent is started.

Contraindications

Known or suspected ischemic heart disease, coronary vasospasm (Prinzmetal variant angina), other serious underlying cardiovascular disease (uncontrolled hypertension), cerebrovascular syndromes, or peripheral vascular ischemia (ischemic bowel disease). Concomitant use with another 5-HT$_1$ receptor agonist within 24 hours. Concomitant use with an ergot alkaloid within 24 hours. Concurrent or recent (within 2 weeks) treatment with an MAOI. Basilar or hemiplegic migraine.

Counseling Points

- Take at first sign of migraine. This drug only treats migraine and will not prevent migraine headaches from occurring. Take exactly as directed; do not redose if no response is achieved.
- Separate doses by at least 2 hours. Maximum of 30 mg per 24-hour period. Maximum of one dose in a 24-hour period for children (6–17 years of age).
- Rizatriptan orally disintegrating tablet is packaged in a blister aluminum pouch. Peel open blister pack

with dry hands right before dosing. Place the tablet on the tongue, allow it to disintegrate, and then swallow. Administration with liquid is not needed.
- Overuse of migraine drugs may cause a worsening of headache or an increase in the frequency of headache
- Report chest pain, confusion, symptoms of a stroke, severe abdominal pain, shortness of breath, or neck/jaw problems since any of these could be signs of problems related to the drug. Do not take the drug again before seeing a healthcare provider.

Key Points

- Rizatriptan should be used only in patients with a clear diagnosis of migraine
- Be familiar with dosage adjustments for patients taking concomitant propranolol
- Be aware of important drug–drug interactions and serious cardiac effects
- Overdosage may worsen headache, be aware of maximum daily doses

Sumatriptan

Brand Names

Imitrex, Sumavel DosePro, Alsuma, Onzetra Xsail, Zembrace SymTouch

Generic Names

Sumatriptan, sumatriptan succinate

Rx Only

Dosage Forms

- Sumatriptan succinate: Film-coated tablet, injection (SUB-Q use only)
- Sumatriptan: Nasal solution, nasal powder

Usage

Acute treatment of migraine in adults with or without aura, acute treatment of cluster headache episodes (SUB-Q injection)

Pregnancy Category C

Dosing

- Oral:
  - Initial dose: 25–100 mg, repeat after 2 hours, if needed
  - Maximum dose: 200 mg/24 hours
- Injectable:
  - Alsuma: 6 mg SUB-Q, repeat in 1 hour, if needed Maximum dose: 6 mg/dose and 12 mg/24 hours
  - Zembrace: 3 mg SUB-Q, may repeat up to 4 times daily (each dose separated by 1 hour) Max dose: 12 mg/24 hours
- Intranasal:
  - Solution: 5–20 mg (10 mg given as one 5 mg spray in each nostril)
    - If headache returns, may repeat dose once after 2 hours
    - Maximum dose: 40 mg/24 hours
  - Powder: A single dose of 22 mg (11 mg nosepiece in each nostril)
    - May repeat dose once after 2 hours
    - Maximum dose: 44 mg/24 hour OR 22 mg/24 hour + one dose of another sumatriptan product
- Renal dosage adjustment: No formal recommendations. Use caution in hemodialysis patients.
- Hepatic dosage adjustment:
  - Bioavailability of oral sumatriptan is increased with liver disease. If treatment is needed, do not exceed single oral doses of 50 mg.
  - Use of all dosage forms is contraindicated with severe hepatic impairment
- Concomitantly with MAOIs: Decreased doses should be considered in injectable form and contraindicated in oral form. Sumatriptan autoinjector should not be used because it is only available as a 6-mg fixed dose.

Adverse Reactions: Most Common

Paresthesias, hot/cold skin sensations, chest discomfort, flushing, fatigue, somnolence, nausea, vomiting, unpleasant taste in mouth, dry mouth, headache, photosensitivity, vertigo, injection-site reactions (with injectable)

Adverse Reactions: Rare/Severe/Important

Chest, jaw, neck tightness, coronary vasospasm, myocardial infarction, arrhythmia, ischemic colitis, blindness and/or vision impairment, seizure, serotonin syndrome, hypertensive crisis

Major Drug Interactions

Drugs Affecting Sumatriptan

Sibutramine, monoamine oxidase inhibitors (MAOIs), ergotamines: Increase risk of serotonin syndrome

Essential Monitoring Parameters

Reduction in migraine headache severity indicates efficacy. ECG should be performed during initial dosing in patients with risk factors for coronary artery disease and among patients who develop signs or symptoms of angina with administration of sumatriptan. Cardiovascular function and risk factors should be monitored at baseline and periodically thereafter.

Contraindications

Ischemic heart disease (angina, myocardial infarction, cerebrovascular accident, transient ischemic attack), peripheral vascular syndromes, uncontrolled hypertension, ischemic bowel disease, severe hepatic impairment (Child-Pugh C), hemiplegic or basilar migraine, hypersensitivity, use of an ergotamine derivative (dihydroergotamine, methysergide) within 24 hours, use of another 5-HT_1 agonist within 24 hours, use of an MAOI within 2 weeks of sumatriptan therapy

Counseling Points

- Take at first sign of migraine. This drug only treats migraine and will not prevent migraine headaches from occurring. Take exactly as directed; do not redose if no response is achieved.
- Follow exact instructions for use. Do not redose if no response is achieved.
- Wear sunscreen and proper clothing when in the sun
- Report any unusual side effects immediately (chest tightness or pain, acute abdominal pain, excessive drowsiness)

Key Points

- Sumatriptan should only be used in patients with a clear diagnosis of migraine
- Demonstrate proper SUB-Q injection technique and syringe/needle disposal
- Be aware of important drug–drug interactions and cardiac effects
- Overdosage may worsen headache; be aware of maximum dose allowance for specific formulation

ANOREXIANTS

Introduction

Obesity is increasing in prevalence worldwide. To be successful in weight loss, it has been suggested that a goal weight should be predefined and a weight loss program should be developed that includes diet, exercise, behavior modification, and, possibly, a pharmacologic agent. Debate continues on the appropriateness of weight loss medications due to the controversy surrounding the deaths and medical complications caused by the combination product Fen-Phen (fenfluramine and phentermine). Phentermine is still available.

Mechanism of Action for the Drug Class

Phentermine is a sympathomimetic amine that stimulates the CNS. It is structurally related to the amphetamines. Phentermine stimulates the CNS and elevates blood pressure. The mechanism of action in treating obesity is unknown.

Members of the Drug Class

In this section: Phentermine; Phentermine/topiramate
Others: Benzphetamine, phendimetrazine, diethylpropion, lorcaserin

◉ Phentermine

Brand Names

Adipex-P, Ionamin, Suprenza, Lomaira

Generic Name

Phentermine

Rx Only

Class IV controlled substance

Dosage Forms

Tablet, capsule, orally disintegrating tablet (ODT)

Usage

Obesity (short-term use)

Pregnancy Category X

Dosing

- Tablet, most formulations: 15–37.5 mg daily (given in 1 to 2 divided doses)
- Tablet (Lomaira only): 8 mg 3 times daily
- ODT formulation: 15–37.5 mg daily in the morning

Adverse Reactions: Most Common

Increased blood pressure, palpitations, arrhythmias, GI discomfort, insomnia, nervousness, and dry mouth

Adverse Reactions: Rare/Severe/Important

Primary pulmonary hypertension, valvular heart disease, psychiatric reactions

Major Drug Interactions

Drugs Affecting Phentermine

Monoamine oxidase inhibitors (MAOIs): Contraindicated due to the risk of severe, possibly fatal adverse reactions

Contraindications

History of cardiovascular disease; hyperthyroidism; glaucoma; history of drug abuse; agitated psychological states; concurrent use or within 14 days following MAOI therapy; pregnancy; breastfeeding

Counseling Points

- Tablet/capsule: Take at breakfast or 1 to 2 hours after breakfast and avoid late night dosing
- ODT: Dissolve on the tongue and take before breakfast

Key Points

- Use for patients with a BMI ≥ 30 kg/m^2 or with patients with a BMI ≥ 27 kg/m^2 in the presence of other risk factors (controlled hypertension, diabetes mellitus, dyslipidemia)
- Should be used in conjunction with a weight management program
- Discontinue if weight loss has not occurred within the first 4 weeks of use
- Use with caution in diabetic patients. Glucose requirements may change.
- Contraindicated in patients with a history of drug abuse, cardiovascular disease, moderate to severe hypertension, pulmonary hypertension, hyperthyroidism, and glaucoma

◉ Phentermine/Topiramate

Brand Name

Qsymia

Generic Name

Phentermine/Topiramate

Rx Only

Class IV controlled substance

Dosage Form

Extended-release capsule

Usage

Obesity

Pregnancy Category X

Dosing

- Initial dose: Phentermine 3.75 mg/topiramate 23 mg once daily increase dose by phentermine 3.75 mg/topiramate 23 mg every 2 weeks
  Max dose: Phentermine 15 mg/topiramate 92 mg
- Renal dosage adjustment: Max dose of phentermine 7.5 mg/topiramate 46 mg (CrCl < 50 ml/min); Avoid in dialysis patients
- Hepatic dosage adjustment: Maximum dose of phentermine 7.5 mg/topiramate 46 mg in moderate impairment

Adverse Reactions: Most Common

Tachycardia, insomnia, cognitive impairment, paresthesia, kidney stones, hypokalemia, risk of hypoglycemia in diabetes patients with weight loss

Adverse Reactions: Rare/Severe/Important

Fetal toxicity, metabolic acidosis, glaucoma, psychiatric disturbances (suicidal ideation)

Major Drug Interactions

Drugs Affecting Phentermine/Topiramate

- Phenytoin, carbamazepine, and lamotrigine: decrease serum concentration of topiramate
- MAO inhibitors: increase hypertensive/cardiovascular effects of phentermine
- Valproic acid: increase serum concentration of topiramate

Phentermine/Topiramate's Effect on Other Drugs

- Carbonic anhydrase inhibitors: increase risk of metabolic acidosis
- Oral contraceptives: decrease efficacy of oral contraceptive

Contraindications

Pregnancy, hyperthyroidism, glaucoma, recent or concurrent MAO inhibitor use

Essential Monitoring Parameter

Monitor for increased heart rate, serum chemistry (especially bicarbonate, potassium, creatinine, glucose)

Counseling Points

- Women of childbearing age must be on two forms of contraception due to the high risk of birth defects
- Drink plenty of fluids to prevent the formation of kidney stones
- Use caution with other CNS medications and alcohol due to increased risk of CNS side effects (most notably, cognitive slowing "brain fog")
- Report tachycardia that lasts for more than a few minutes

Key Points

- Qsymia is a combination product of phentermine (an appetite stimulant) and topiramate (an anticonvulsant whose common side effect is weight loss)
- Use for patients with a BMI ≥ 30 kg/m^2 or with patients with a BMI ≥ 27 kg/m^2 in the presence of other risk factors (controlled hypertension, diabetes mellitus, dyslipidemia)
- Use in conjunction with a weight management program
- Negative pregnancy test is required prior to initiation of therapy and monthly while on therapy
- Discontinue 15 mg/92 mg dose gradually to prevent possible seizure
- Restricted drug access program: REMS registration required. For a listing of certified pharmacies approved to dispense Qsymia, refer to http://www.qsymiarems.com/certified-pharmacy-network.htm

BENZODIAZEPINES

Introduction

Benzodiazepines are utilized in a broad spectrum of CNS disorders, though primarily as antianxiety, anticonvulsant, or hypnotic agents. Benzodiazepines are Schedule IV medications and may be habit forming. If patients use a benzodiazepine long-term, they should be counseled not to discontinue it abruptly. A gradual taper is required to avoid rebound, relapse, and withdrawal symptoms. The agents within this class have many similarities, and the differences between them are mostly pharmacokinetic.

Mechanism of Action for the Drug Class

Benzodiazepines facilitate the activity of the inhibitory neurotransmitter GABA (gamma-aminobutyric acid) and other inhibitory transmitters by binding to specific benzodiazepine receptors, resulting in sedative, hypnotic, anxiolytic, anticonvulsant, and muscle relaxant properties.

Adverse Reactions for the Drug Class: Most Common

Sedation, somnolence, memory impairment, coordination problems, dizziness, dysarthria, anterograde amnesia, and paradoxical reactions (especially in pediatric or elderly patients)

Adverse Reactions for the Drug Class: Rare/Severe/Important

Withdrawal syndrome and respiratory depression (especially additive with other CNS depressants and alcohol)

Counseling Points for the Drug Class

- Avoid alcohol because it can lead to possibly fatal respiratory depression
- Avoid activities that require mental alertness (e.g., driving) until the effects of the medication are known and comfortable and whenever the dose is increased
- Avoid abrupt discontinuation

Key Points for the Drug Class

- **Black BoxWarning:**
  - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.
- Benzodiazepines are Schedule IV medications that may be habit forming. Be cautious using benzodiazepines in patients with a history of substance abuse.
- Abrupt discontinuation should be avoided and a tapering strategy should be utilized to prevent withdrawal symptoms (e.g. seizures), especially in patients with pre-existing seizure disorders and in patients who receive chronic benzodiazepine therapy
- Benzodiazepines are contraindicated in acute narrow-angle glaucoma and not recommended in pregnancy

Members of the Drug Class

In this section: Alprazolam, clonazepam, diazepam, lorazepam

Others: Chlordiazepoxide, clorazepate, midazolam, oxazepam, estazolam, quazepam, triazolam, midazolam

◉ Alprazolam

Brand Names

Xanax, Xanax XR, Alprazolam Intensol

Generic Name

Alprazolam

Rx Only

Class IV controlled substance

Dosage Forms

Tablet, extended-release tablet, orally disintegrating tablet (ODT), solution

Usage

Anxiety disorders, panic disorders

Pregnancy Category D

Dosing

- Initial dose:
  - Anxiety: 0.25–0.5 mg 3 times daily
  - Panic disorders: 0.5 mg 3 times daily

Major Drug Interactions

Major substrate of CYP3A4

Drugs Affecting Alprazolam

- CNS depressants and alcohol: Increase CNS depression
- CYP3A4 Inhibitors: Increase serum concentrations (contraindicated with ketoconazole, itraconazole, or other potent CYP3A4 inhibitors)

Contraindications

Narrow-angle glaucoma, concurrent use with potent CYP3A4 inhibitors

Essential Monitoring Parameters

Respiratory depression, cardiovascular status, increase in fall risk (especially in the elderly)

Counseling Points

- Do not chew, crush, or break extended-release tablets. Swallow whole.
- Do not push ODTs through the blister pack foil. Peel back foil, remove tablet with dry finger, and place the tablet on tongue. Medication does not require water.
- Alprazolam may cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks that require mental alertness (e.g., driving or operating machinery).

Key Points

- **Black Box Warning:**
  - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.
- Abuse potential may be higher with this agent compared with other benzodiazepines due to its quicker onset of action

Temazepam

Brand Name

Restoril

Generic Name

Temazepam

Rx Only

Class IV controlled substance

Dosage Form

Capsule

Pregnancy Category X

Usage

Short-term treatment of insomnia, anxiety

Dosing

Insomnia: 7.5–30 mg at bedtime

Adverse Reactions: Most Common

Sedation, somnolence, memory impairment, coordination problems, dizziness, emergence of complex behavior ("sleep driving")

Adverse Reactions: Rare/Severe/Important

Withdrawal syndromes and respiratory depression (especially additive with other CNS depressants or alcohol)

Major Drug Interactions

Temazepam's Effect on Other Drugs

CNS depressants: Additive CNS depression

Contraindications

Narrow-angle glaucoma, pregnancy

Essential Monitoring Parameters

Respiratory rate, cardiovascular status, increase in fall risk (especially in the elderly)

Counseling Points

- Ingesting alcoholic beverages during benzodiazepine therapy is very dangerous and must be avoided
- Take just before going to sleep and only when able to get a full night's sleep (i.e., 7 to 8 hours)
- Take only when needed and should be used for a short term (7 to 10 days) to prevent habit-forming use

Key Points

- **Black Box Warning:**
  - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.
- Elderly patients are the most susceptible to adverse effects and should be started with the 7.5 mg dose

Clonazepam

Brand Names

Klonopin

Generic Name

Clonazepam

Rx Only

Class IV controlled substance

Dosage Forms

Tablet, orally disintegrating tablet (ODT)

Usage

Panic disorder, seizures (Lennox-Gastaut, akinetic, myoclonic, absence), restless leg syndrome, social phobia, acute mania associated with bipolar, multifocal tic disorders

Pregnancy Category D

Dosing

- Seizure disorders:
  - Initial: 0.25–0.5 mg 3 times daily
  - Maximum dose: 20 mg daily
- Panic disorders:
  - 0.25–0.5 mg twice or 3 times daily
  - Maximum dose: 4 mg daily
- Hepatic dosage adjustment: Contraindicated in severe hepatic disease

Major Drug Interactions

Major substrate of CYP3A4

Drugs Affecting Clonazepam

- Phenytoin, carbamazepine, and phenobarbital: Decrease serum concentrations
- CYP3A4 Inhibitors (e.g., ketoconazole, itraconazole, clarithromycin): Increase serum concentrations
- CNS depressants and alcohol: Increase CNS depression

Contraindications

Narrow-angle glaucoma, severe hepatic impairment

Essential Monitoring Parameters

CBC, liver, and renal function tests (periodically with long-term therapy), suicidality (e.g., suicidal thoughts, depression, behavioral changes), respiratory depression

Counseling Point

Do not push ODTs through the blister pack foil. Peel back foil, remove tablet with dry finger, and place the tablet on tongue. Medication does not require water.

Key Points

- **Black Box Warning:**
  - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.
- Some clinicians use once-daily bedtime dosing due to the drug's long half-life
- Abrupt discontinuation should be avoided to prevent withdrawal symptoms, especially in patients with seizure disorders to prevent precipitating seizures
- During withdrawal of clonazepam in patients with seizure disorders, another anticonvulsant may be indicated for simultaneous substitution

◉ Diazepam

Brand Names

Valium, Diastat Pediatric, Diazepam Intensol, Diastat AcuDial

Generic Name

Diazepam

Rx Only

Class IV controlled substance

Dosage Forms

Tablet, concentrate, injection, rectal gel

Usage

Anxiety disorders, acute alcohol withdrawal, seizures (adjunctive therapy, status epilepticus), skeletal muscle relaxant, preoperative and procedural sedation, and amnesia

Pregnancy Category D

Dosing

- Anxiety disorders: Initial dose of 2–10 mg PO 2 to 4 times daily, as needed
- Skeletal muscle relaxant (adjunct therapy): Initial dose of 2–10 mg PO 3 to 4 times daily
- Acute alcohol withdrawal: Initial dose of 5–10 mg PO 3 to 4 times daily, as needed or 10 mg IV/IM initially
- Status epilepticus:
  - Initial dose: 5–10 mg IV every 5 to 10 minutes
  - Maximum dose: 30 mg

Major Drug Interactions

Major Substrate of CYP2C19 and CYP3A4

Drugs Affecting Diazepam

- CNS depressants and alcohol: Increase CNS depression
- CYP3A4 Inhibitors: Increase serum concentrations (contraindicated with ketoconazole and itraconazole)
- CYP2C19 Inhibitors (e.g., fluoxetine, fluconazole); increase serum concentrations

Contraindications

Myasthenia gravis, acute narrow-angle glaucoma, untreated open-angle glaucoma, sleep apnea syndrome, severe respiratory insufficiency, severe hepatic insufficiency

Essential Monitoring Parameters

Heart rate, respiratory rate, blood pressure, and mental status; liver enzymes and CBC with long-term therapy, respiratory depression, increase in fall risk (especially in the elderly)

Key Points

- **Black Box Warning:**
  - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.
- Not recommended in the elderly due to its long half-life
- Abrupt discontinuation should be avoided to prevent withdrawal symptoms, especially in patients with seizure disorders to prevent precipitating seizures

◉ Lorazepam

Brand Names
Ativan, Lorazepam Intensol

Generic Name
Lorazepam

Rx Only
Class IV controlled substance

Dosage Forms
Tablet, concentrate, injection

Pregnancy Category D

Usage
Anxiety disorders, seizures (status epilepticus), agitation in the intensive care unit patient, insomnia, acute alcohol withdrawal syndrome, agitation, antiemetic

Dosing
- Anxiety disorders: Initial dose of 2–3 mg daily in 2 to 3 divided doses
- Status epilepticus:
  - Initial dose: 4 mg IV can repeat in 5 to 15 minutes
- Acute alcohol withdrawal: Initial dose of 1–4 mg IV/PO as needed (dose determined by a validated severity assessment scale)
- IV sedation in ICU setting (dose determined by a validated severity assessment scale):
  - Intermittent: Initial IV loading dose of 2 mg IV and then an initial maintenance dose of 0.02–0.06 mg/kg every 2 to 6 hours as needed
  - Continuous IV infusion: Initial dose of 0.01–0.1 mg/kg per hour (maximum dose of 7 mg/hour or < 10 mg/hour)

Major Drug Interactions
Drugs Affecting Lorazepam
- CNS depressants and alcohol: Increase CNS depression
- Valproic acid and probenecid: Increase serum levels (reduce lorazepam dose by 50%)

Contraindications
Acute narrow-angle glaucoma, sleep apnea (with parenteral formulation), severe respiratory insufficiency (except during mechanical ventilation)

Essential Monitoring Parameters
Respiratory and cardiovascular status, blood pressure, heart rate, symptoms of anxiety
CBC, liver function tests; clinical signs of propylene glycol toxicity (for continuous high-dose and/or long duration intravenous use) including serum creatinine, BUN, serum lactate, osmol gap)

Key Points
- **Black Box Warning:**
  - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.
- There is a risk of propylene glycol toxicity with the parenteral formulation; monitor closely when using higher doses or for prolonged periods of time (e.g., continuous infusion of ≥ 6 mg/hour for 48 hours)
- Although specific dose recommendations are not available, use with caution in patients with renal or hepatic impairment
- Abrupt discontinuation should be avoided to prevent withdrawal symptoms, especially in patients with seizure disorders to prevent precipitating seizures

NONBENZODIAZEPINE ANTIANXIETY AGENTS

Introduction
Buspirone is the only drug within this class. Although used for anxiety disorders, it is not a benzodiazepine and is chemically unrelated to other CNS agents. Unlike benzodiazepines, it lacks anticonvulsant and sedative properties and, therefore, has less overall clinical utility. However, buspirone lacks issues that can be problematic with benzodiazepine use. Buspirone is less sedating, has fewer CNS side effects, and has a higher threshold of interaction with other CNS depressants and alcohol. Physical dependency and withdrawal symptoms have not been seen with buspirone. Buspirone can be a good maintenance agent for patients who cannot tolerate benzodiazepines due to undesirable side effects and interactions, patients with a history of drug or alcohol abuse, and the elderly.

Mechanism of Action for the Drug Class

Buspirone's mechanism of action is primarily unknown. The drug has a high affinity for serotonin receptors and a moderate affinity for dopamine type-2 receptors; it is this action that is thought to potentiate its anxiolytic and antidepressant effects.

Members of the Drug Class

In this section: Buspirone

◉ Buspirone

Brand Name

BuSpar (no longer available as a brand product, only generic)

Generic Name

Buspirone

Rx Only

Dosage Form

Tablet

Usage

Generalized anxiety disorders, depression (augmentation agent), aggression, depression, premenstrual syndrome

Pregnancy Category B

Dosing

Generalized anxiety disorder

- Initial dose: 7.5 mg twice daily
- Dosage adjustments: Titrate by 2.5 mg twice daily every 2 to 3 days to a maximum dose of 60 mg daily (target for most patients is 10-15 mg twice daily)
- Renal dosage adjustment: Use is not recommended in patients with severe renal dysfunction
- Hepatic dosage adjustment: Use is not recommended in patients with severe hepatic dysfunction

Adverse Reactions: Most Common

Dizziness, lightheadedness, headache, nausea, nervousness, excitement

Adverse Reactions: Rare/Severe/Important

Extrapyramidal symptoms, restless leg syndrome

Major Drug Interactions

Major substrate of CYP3A4

Drugs Affecting Buspirone

- Erythromycin, cimetidine, ketoconazole, itraconazole, clarithromycin, diltiazem, verapamil, other 3A4 inhibitors: Increase serum levels
- Rifampin, phenytoin, phenobarbital, carbamazepine, fluoxetine: Decrease serum levels

Buspirone's Effect on Other Drugs

- Monoamine oxidase inhibitors (MAOIs): Warning of concomitant use due to risk of hypertensive crisis
- Haloperidol: Increases serum levels

Essential Monitoring Parameters

Mental status, symptoms of anxiety

Counseling Points

- Antianxiety effects may not be seen for at least a week or more
- Buspirone should not be stopped abruptly
- Avoid large quantities of grapefruit juice

Key Points

- Abuse potential is low compared with benzodiazepines
- Buspirone will not treat benzodiazepine withdrawal symptoms
- Because of the delayed onset of action, buspirone cannot be used to treat acute anxiety

ANTICONVULSANTS

Introduction

Anticonvulsants are used for a broad spectrum of CNS on- and off-label indications, including seizure disorders, trigeminal and postherpetic neuralgias, bipolar disorders, neuropathic pain, migraine, mood disorders, and many others. The treatment goal in epilepsy is seizure-free control on as few antiepileptic drugs (AEDs) as possible with few to no side effects. However, achieving a balance between superior efficacy and side effects is not easily obtainable for many patients due to the many adverse reactions affiliated with these medications. In addition, the FDA has issued a special drug class warning of increased suicide behavior or ideation for all AEDs. Patients and family members should be made aware of the increased risk of suicidal thoughts and behavior. With any AED, patients should check with their prescriber before discontinuing medication. A gradual taper in dose may be required to prevent seizures and status epilepticus. Many AEDs are a substrate of or strongly inhibit/induce the CYP enzymatic system, resulting in

multiple drug interactions. In addition, pregnant patients who remain on AEDs should be encouraged to enroll in the North American Antiepileptic Drug Pregnancy Registry.

Mechanism of Action for the Drug Class

Multiple mechanisms of action exist within this drug class and, in many cases, are unknown. Effective seizure control typically augments CNS inhibitory processes or opposes excitatory processes. Generally, when used for seizure disorders, control is achieved through alteration of sodium, calcium, and/or potassium ion channels and/or neurotransmitters, including potentiating inhibitory gamma-aminobutyric acid (GABA) and antagonizing excitatory glutamate. The mechanism may be through direct activation/inhibition of an ion channel, receptor site, or changes in enzyme production, metabolism, or function.

Members of the Drug Class

In this section: Carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, valproic acid, zonisamide, and derivatives

Others: Brivaracetam, eslicarbazepine, ethosuximide, ezogabine, felbamate, fosphenytoin, methsuximide, pentobarbital, perampanel, primidone, rufinamide, tiagabine, vigabatrin

◉ Carbamazepine

Brand Names

Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR

Generic Name

Carbamazepine

Rx Only

Dosage Forms

Tablet, extended-release tablet, chewable tablet, extended-release capsule, suspension

Usage

Seizures (partial, generalized tonic-clonic seizures, and mixed types); neuropathic pain; acute manic and mixed episodes associated with bipolar 1 disorder (Equetro only); psychiatric disorders (unipolar depression, schizoaffective disorder, resistant schizophrenia, post-traumatic stress disorder); restless leg syndrome; many others

Pregnancy Category D

Dosing

- Seizure disorders in adults and children > 12 years of age:
  - Initial dose:
    - Tablet or capsule: 200 mg twice a day
    - Suspension: 50 mg 4 times a day
  - Dosage adjustment: Increase at weekly intervals by ≤ 200 mg daily in divided doses until optimal control is attained
  - Usual maintenance dose: 800–1200 mg a day
- Trigeminal neuralgia:
  - Initial dose:
    - Extended-release capsule: 200 mg once daily
    - Tablet or capsule: 100 mg twice daily
    - Suspension: 50 mg 4 times a day
  - Dosage adjustment: Increase by up to 200 mg/day in divided dosing as needed (extended-release capsule should be dosed twice daily, if total daily dose > 200 mg)
  - Maximum dose: Do not exceed 1200 mg/day
- Acute mania and mixed episodes with bipolar 1 disorder (Equetro only):
  - Initial dose: 200 mg twice a day
  - Dosage adjustment: Increase daily dose in increments of 200 mg/day until optimal response is achieved
  - Maximum dose: 1600 mg/day

Pharmacokinetic Monitoring

Target serum concentrations: 4–12 µg/ml

Adverse Reactions: Most Common

Dizziness, drowsiness, ataxia, nausea, vomiting, diplopia, headache

Adverse Reactions: Rare/Severe/Important

Hematologic reactions (aplastic anemia, leukopenia, agranulocytosis, eosinophilia, thrombocytopenia), hepatic, dermatologic reactions (toxic epidermal necrolysis, Stevens-Johnson syndrome), syndrome of inappropriate antidiuretic hormone (SIADH), cardiac conduction disturbances, hyponatremia, osteomalacia (chronic administration)

Major Drug Interactions

Drugs Affecting Carbamazepine

- Carbamazepine induces its own metabolism
- Cimetidine, erythromycin, clarithromycin, fluoxetine, valproic acid, protease inhibitors, azole antifungals, isoniazid, diltiazem, verapamil, and others: Increase carbamazepine serum concentrations
- Phenobarbital, primidone, rifampin, theophylline, and phenytoin: Decrease serum concentrations of carbamazepine

Carbamazepine's Effect on Other Drugs

Carbamazepine decreases the serum concentrations of many drugs, which can lead to therapeutic failure, including the following: apixaban, caspofungin, cyclosporine, dabigatran, edoxaban, felbamate, lamotrigine, 10-monohydroxy metabolite (active metabolite of oxcarbazepine), phenytoin, protease inhibitors, rivaroxaban, tiagabine, topiramate, valproic acid, zonisamide, oral contraceptives, theophylline, warfarin, and many others

Contraindications

Carbamazepine should not be used in patients with a history of previous bone marrow dyscrasias. Since carbamazepine is structurally similar to tricyclic antidepressants, carbamazepine should be avoided in patients with known hypersensitivity to these agents. Likewise, patients should be discontinued from their MAOI for 14 days prior to starting carbamazepine. Coadministration of carbamazepine with nefazodone is contraindicated.

Essential Monitoring Parameters

Serum carbamazepine concentrations, CBC, platelets, serum sodium, liver function tests

Counseling Points

- Do not crush or chew extended-release tablets or capsules. Extended-release tablet coating is not absorbed and is excreted in the feces. Tablet coatings may be noticeable in the stool. Capsules may be opened and sprinkled over applesauce.
- Notify your healthcare provider if any of the following symptoms occur: unusual bleeding, bruising, fever, sore throat, rash, ulcer in the mouth, muscle cramping, jaundice, or suicidal thoughts
- If using oral contraceptives, consider an additional or alternative method of birth control
- May cause drowsiness, dizziness, or blurred vision. Observe caution when driving or performing tasks requiring alertness, coordination, or physical dexterity until the effects of the medication are familiar.
- Do not drink alcohol because it can exacerbate CNS depression, somnolence, and dizziness

Key Points

- **Black Box Warnings:**
  - Carbamazepine can lead to serious dermatologic reactions, including toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome. There is a higher incidence in patients of Asian descent with the HLA-B*1502 allele. These patients should be screened for the presence of the HLA-B*1502 allele. If positive, carbamazepine should not be started.
  - Carbamazepine can lead to aplastic anemia and agranulocytosis
- Carbamazepine is metabolized through CYP3A4 to an active metabolite, 10,11-epoxide. The active metabolite is metabolized through epoxide hydrolase. Carbamazepine is a strong inducer of CYP450 enzymes and P-glycoprotein. Be alert to any new medications added or discontinued from a patient's drug regimen because this could affect medication blood levels or the levels of the active metabolite.
- Because of autoinduction, the half-life of the drug and its serum levels may change over the first few weeks of therapy. Patients must be observed closely and dosing must be individualized.

Gabapentin

Brand Names

Neurontin, Gralise, Horizant

Generic Names

Gabapentin, gabapentin enacarbil

Rx Only

Dosage Forms

Tablet, extended-release tablet, capsule, solution

Usage

Seizures (adjunctive therapy in the treatment of partial seizures with and without secondary generalization), *postherpetic neuralgia, pain (neuropathic, chronic, and postoperative pain), diabetic peripheral neuropathy, restless leg syndrome,* vasomotor symptoms associated with menopause, fibromyalgia, social phobia, and many others

Pregnancy Category C

Dosing

- Adjunctive therapy for partial seizures and diabetic peripheral neuropathy with immediate-release formulation (Neurontin):
  - Initial therapy: 300 mg 3 times daily
  - Dosage adjustment: Increase at weekly intervals to 1.8 g daily
  - Maximum dose: Up to 3.6 g daily
- Neuropathic pain: (postherpetic neuralgia, diabetic neuropathy)
  - Immediate-release (Neurontin) Initiate therapy with 300 mg on day 1300 mg twice a day on day 2, and 300 mg 3 times a day on day 3. Titrate dose as needed for pain relief up to a daily dose of 1.8 g. (Doses as high as 3.6 g/day have been used in diabetic nephropathy.)
  - Extended-release (Gralise) initial dose: Initiate therapy with 300 mg once a day on day 1, titrate up to 600 mg once a day on day 2900 mg once daily on days 3 to 6, 1200 mg once daily on days 7 to 10, 1500 mg once daily on days 11 to 14, and 1800 mg once daily thereafter
  - Extended-release (Horizant) initial dose: Initiate therapy with 600 mg once daily in the morning for 3 days, then increase to 600 mg twice daily beginning on day 4
- Restless leg syndrome:
  - Immediate-release:
    - Initial therapy: Initiate therapy with 300 mg once daily 2 hours prior to bedtime
    - Dosage adjustment: Dose may be titrated up every 2 weeks until symptom relief

- Maintenance therapy: Typically, 300–1800 mg daily; doses > 600 mg daily are given in divided doses
- Extended-release (Horizant): Initiate therapy with 600 mg once daily (5 PM) and titrate up to 1200 mg daily

- Renal dosage adjustment:
  - Immediate-release:
    - CrCl ≥ 60 ml/min: 300–1200 mg 3 times a day
    - CrCl > 30–59 ml/min: 200–700 mg twice a day
    - CrCl > 15–29 ml/min: 200–700 mg once daily
    - CrCl 15 ml/min: 100–300 mg once daily
    - CrCl <15 ml/min: Reduce daily dose in proportion to CrCl of 15 ml/min
    - End-stage renal disease (ESRD) or hemodialysis (HD): Utilize dosing of CrCl <15 ml/min plus give an additional supplemental dose of 125–350 mg post-HD
  - Extended-release:
    - CrCl ≥ 60 ml/min: 1800 mg once daily
    - CrCl 30–59 ml/min: 600–1800 mg once daily
    - CrCl 15-29 ml/min: 300–600 mg daily
    - CrCl <15: 300 mg every other day to 300 mg daily max
    - ESRD or HD: Not recommended

Adverse Reactions: Most Common

Fatigue, somnolence, dizziness, peripheral edema, weight gain

Adverse Reactions: Rare/Severe/Important

Aggressive behavior in children, nystagmus, ataxia

Major Drug Interactions

Drugs Affecting Gabapentin

Aluminum-containing antacids: Decrease bioavailability by 20%

Essential Monitoring Parameter

Serum creatinine

Counseling Points

- Do not drink alcohol because it can exacerbate CNS depression, somnolence, and dizziness
- Avoid driving or operating heavy machinery until you are aware of how gabapentin will affect you

Key Points

- Upon discontinuation of therapy, reduce dose gradually to avoid precipitating seizure activity
- Immediate-release (Neurontin) and extended-release (Gralise, Horizant) are not interchangeable products due to differences in formulation, indication, and pharmacokinetics
- Renal dosing adjustments are necessary

Lacosamide

Brand Name

Vimpat

Generic Name

Lacosamide

Rx Only

Schedule V controlled substance

Dosage forms

Tablets, solution, injection

Usage

Monotherapy or adjunctive therapy for partial-onset seizures, refractory status epilepticus

Pregnancy Category C

Dosing

- Monotherapy: 100 mg BID, increase by 50 mg every week to max of 200 mg BID
- Adjunctive therapy: 50 mg BID increase by 50 mg every week to max 200 mg BID
- Refractory status epilepticus: 400 mg intravenous loading dose, then 200 mg BID
- Renal adjustment: Max dose 300 mg/day (CrCl < 30 ml/min). Dialysis patients may need supplemental dose of up 50% of dose.
- Hepatic impairment: Max dose 300 mg/day (mild-to-moderate hepatic impairment); avoid use in severe hepatic impairment

Adverse Reactions: Most Common

Diplopia, headache, dizziness

Adverse Reactions: Rare/Severe/Important

Suicidal behavior or ideation, cardiac arrhythmia (PR prolongation), multiorgan hypersensitivity reaction

Major Drug Interactions

Beta-blockers and calcium channel blockers given with lacosamide may prolong the PR interval, possibly causing bradycardia or AV block. Obtain ECG before beginning lacosamide and after maximum dose is achieved.

Contraindications

None

Essential Monitoring Parameters

ECG in high-risk patients (patients with cardiac disease or on beta-blockers or calcium channel blockers) and during intravenous lacosamide administration

Counseling Points

- May cause irregular heartbeat or may cause fainting
- Watch for dizziness, double vision, difficulty with coordination or walking

Key Points

- Lacosamide has gained favor as an antiepileptic given its lack of drug interactions with other antiepileptics
- When transitioning from another antiepileptic to lacosamide, allow for a 3-day overlap before discontinuing the previous antiepileptic
- Intravenous and oral dosing are the same

Lamotrigine

Brand Names

Lamictal, Lamictal XR, Lamictal CD, Lamictal ODT

Generic Name

Lamotrigine

Rx Only

Dosage Forms

Tablet, extended-release tablet, chewable dispersible tablet, orally disintegrating tablet (ODT). Starter kits are available for initial dosing titration when patients are already receiving valproic acid (blue kit) or carbamazepine, phenytoin, phenobarbital, primidone, or rifampin (green kit). The orange starter kit is used when titration is not affected by other concomitant medication.

Usage

Adjunctive therapy for seizures (generalized seizures of Lennox-Gastaut syndrome, partial seizures, and primary generalized tonic-clonic seizures); conversion to monotherapy for partial seizures in patients who are currently taking valproic acid, carbamazepine, phenobarbital, phenytoin, or primidone as the single AED), maintenance treatment of bipolar 1 disorder

Pregnancy Category C

Dosing

- Seizure disorders (adjunctive therapy) and bipolar disorder:
  - Initial dosing and titration schedules depend on concomitant medications. Initiating at a higher dose or titrating at an accelerated rate increases the incidence of lamotrigine-associated rash.
    - Concurrent use with valproic acid: Initial dose is 25 mg every other day for 1 to 2 weeks
    - Concurrent use with carbamazepine, phenobarbital, phenytoin, primidone, or rifampin: Initial dose is 50 mg a day for 1 to 2 weeks
    - Concurrent use with any other AED: Initial dose is 25 mg daily for 1 to 2 weeks
  - Dosage adjustments: Follow specific dosing guidelines for titration beyond weeks 1 to 2
- Seizure disorders (conversion to monotherapy): Follow specific guidelines to appropriately titrate lower doses of valproic acid, carbamazepine, phenobarbital, phenytoin, and primidone, while increasing doses of lamotrigine
- Hepatic dosage adjustment: Reduce dosing by 25% to 50% and titrate to clinical effectiveness in moderate-to-severe hepatic impairment

Adverse Reactions: Most Common

Headache, dizziness, rash, diplopia, nausea, somnolence, ataxia, rhinitis, blurred vision, somnolence

Adverse Reactions: Rare/Severe/Important

Life-threatening dermatologic reactions (toxic epidermal necrolysis, Stevens-Johnson syndrome), hypersensitivity reactions, multiorgan failure/dysfunction, blood dyscrasias, aseptic meningitis

Major Drug Interactions

Drugs Affecting Lamotrigine

- Valproic acid: Increases lamotrigine concentrations and effects
- Oral contraceptives, rifampin, carbamazepine, phenytoin, primidone, oxcarbazepine, and phenobarbital: May decrease lamotrigine concentrations

Counseling Points

- Women should alert their physician if they plan on starting or stopping oral contraceptives. Levels of lamotrigine can fluctuate greatly for weeks "on" the pill versus weeks "off" the pill.
- It is very important to slowly increase daily dosage as directed. Use a calendar to assist in this process.
- Notify your healthcare provider immediately if you develop a rash

Key Points

- **Black Box Warning:**
  - Lamotrigine may cause life-threatening serious rashes, including toxic epidermal necrolysis or Stevens-Johnson syndrome. The risk of rash is increased in children, with concomitant use with valproic acid, with doses greater than the recommended initial dose, and when upward dose titration occurs too quickly. Patients should always be monitored for rash when starting therapy with this agent.
- Do not rechallenge a patient with lamotrigine if a rash has occurred with prior use

Levetiracetam

Brand Names

Keppra, Keppra XR

Generic Name

Levetiracetam

Rx Only

Dosage Forms

Tablet, extended-release tablet, solution, injection

Usage

Seizures (adjunctive therapy for partial, myoclonic, and primary generalized tonic-clonic), status epilepticus, manic bipolar 1 disorder, migraine prophylaxis

Pregnancy Category C

Dosing

- Immediate release:
  - Initial dosing: 500 mg twice a day
  - Dosage adjustment: Titrate every 2 weeks up to 1500 mg twice a day
- Extended release:
  - Initial dosing: 1000 mg daily
  - Dosage adjustment: Titrate every 2 weeks up to 3000 mg once daily
- Renal dosage adjustment:
  - Immediate-release:
    - CrCl < 80 ml/min: 500–1500 mg twice daily
    - CrCl 50–80 ml/min: 500–1000 mg twice daily
    - CrCl 30–50 ml/min: 250–750 mg twice daily
    - CrCl < 30 ml/min: 250–500 mg twice daily
    - ESRD on HD: 500–1000 mg daily with a supplemental dose of 250–500 mg after HD
  - Extended release:
    - CrCl > 80 ml/min: 1000–3000 daily
    - CrCl 50–80 ml/min: 1000–2000 mg daily
    - CrCl 30–50 ml/min: 500–1500 mg daily
    - CrCl < 30 ml/min: 500–1000 mg daily
    - ESRD on HD: Use immediate-release formulation

Adverse Reactions: Most Common

Asthenia, somnolence dizziness, infection, decreased appetite, vomiting

Adverse Reactions: Rare/Severe/Important

Behavior abnormalities (depression, nervousness, mood swings, irritability, agitation); Serious dermatologic reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); Coordination difficulties; increased diastolic blood pressure (young children) hematologic abnormalities (e.g., reduced RBC, hemoglobin, or WBC)

Essential Monitoring Parameters

Serum creatinine, CBC

Counseling Points

- May cause drowsiness, dizziness, changes in mood
- Use caution when driving or performing tasks requiring alertness, coordination, or physical dexterity
- Report any signs of rash, severe weakness, problems with muscle coordination (difficulty walking and moving)

Key Points

- Levetiracetam is a relatively well-tolerated antiepileptic and its major advantage is its lack of drug interactions
- Reduced drug levels can occur during pregnancy. Close monitoring is recommended.
- Patients should be monitored for changes in mood or behavior.
- Discontinue gradually to reduce risk of increased seizure frequency.

Oxcarbazepine

Brand Name

Trileptal, Oxtellar XR

Generic Name

Oxcarbazepine

Rx Only

Dosage Forms

Tablet, extended-release tablet, suspension

Usage

Seizures (monotherapy and adjunctive therapy in partial seizures), bipolar disorders, neuropathic pain

Pregnancy Category C

Dosing

Immediate Release:

- Initial dose: 300 mg twice a day. Titrate dose up by 600 mg daily once a week to recommended dose of 600 mg twice a day.
- Renal dosage adjustment: If CrCl < 30 ml/min, initiate dose at 150 mg twice a day

Extended Release:

- Initial dose 600 once daily. Titrate dose up by 600 mg daily once a week to recommended dose of 1200 mg to 2400 mg once daily
- Renal dosage adjustment: If CrCl < 30 ml/min, initiate dose at 300 mg daily. ESRD (on dialysis) immediate-release formulations should be used in place of extended-release formulation.

Adverse Reactions: Most Common

Dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, abnormal gait

Adverse Reactions: Rare/Severe/Important

Hyponatremia, anaphylactic reactions and angioedema, multiorgan hypersensitivity reactions, dermatologic reactions (TEN and/or Stevens-Johnson syndrome), psychomotor slowing, bone marrow dyscrasias

Major Drug Interactions

Drugs Affecting Oxcarbazepine

Phenobarbital, carbamazepine, valproic acid, phenytoin, and verapamil: Decrease serum concentrations of MHD (active metabolite), compromising effectiveness

Oxcarbazepine's Effect on Other Drugs

- Decreases serum concentrations of oral contraceptives, felodipine, and lamotrigine
- Increases serum concentrations of phenytoin and phenobarbital

Essential Monitoring Parameters

Sodium

Counseling Points

- If using oral contraceptives, consider an additional or alternative method of birth control
- May cause drowsiness, dizziness, or blurred vision. Observe caution when driving or performing tasks requiring alertness, coordination, or physical dexterity.
- Do not drink alcohol because it can exacerbate CNS depression, somnolence, and dizziness

Key Points

- Of patients with a history of a hypersensitivity reaction to carbamazepine, approximately 25% to 30% experience a hypersensitivity reaction to oxcarbazepine
- Unlike carbamazepine, oxcarbazepine has not been shown to cause autoinduction

◉ Phenobarbital

Generic Name

Phenobarbital

Rx Only

Class IV controlled substance

Dosage Forms

Tablet, capsule, elixir, injection

Usage

Sedative/hypnotic, *seizure disorders* (partial and generalized tonic-clonic seizures, status epilepticus)

Pregnancy Category D

Dosing

- Seizure disorders:
  - Loading dose: 10–20 mg/kg
  - Initial dose: 1–3 mg/kg per day
- Sedation: Initial dose of 30–120 mg daily in divided doses
- Renal dosage adjustment: If CrCl < 10 ml/min, administer doses every 12 to 16 hours
- Hepatic dosage adjustment: Reduce dose in hepatic impairment; contraindicated in severe liver dysfunction

Pharmacokinetic Monitoring

Target serum concentration: 10–40 µg/ml

Adverse Reactions: Most Common

Fatigue, drowsiness, decreased cognitive function, hyperactivity in children

Adverse Reactions: Rare/Severe/Important

Respiratory depression (contraindicated in severe respiratory disorders), hepatotoxicity (contraindicated in severe liver dysfunction), rash (including Stevens-Johnson syndrome), osteomalacia (chronic administration), acute intermittent porphyria (contraindicated in porphyria), hematologic disorders

Major Drug Interactions

Drugs Affecting Phenobarbital

- Cimetidine, felbamate, valproic acid: Increase serum concentrations

Phenobarbital's Effect on Other Drugs

- Phenobarbital decreases serum concentrations of and may lead to therapeutic failure of many drugs, including apixaban, carbamazepine, dabigatran, lamotrigine, rivaroxaban, theophylline, verapamil, valproic acid, warfarin, and zonisamide
- Phenobarbital decreases efficacy of oral contraceptives and metronidazole

Essential Monitoring Parameters

Phenobarbital serum concentrations, liver function tests, serum creatinine

Counseling Points

- May cause drowsiness. Use caution when driving or performing tasks requiring alertness, coordination, or physical dexterity. Avoid use with other CNS depressants, including alcohol, to prevent excessive sedation.
- If using oral contraceptives, consider an additional or alternative method of birth control

Key Points

- Due to phenobarbital's strong inducing influence on the CYP450 enzymatic system, be alert to any new medications added or discontinued from a patient's drug regimen because it could affect medication concentrations
- The half-life of this drug is approximately 80 hours. Maintenance dosing can be given at bedtime to decrease daytime sedation.

Phenytoin

Brand Names

Dilantin, Dilantin-125, Phenytek, Dilantin Infatab

Generic Name

Phenytoin

Rx Only

Dosage Forms

Capsule, extended-release capsule, chewable tablet, suspension, injection

Usage

Seizures (generalized tonic-clonic and complex partial seizures and prevention and treatment of seizures occurring during or following head trauma/neurosurgery, status epilepticus)

Pregnancy Category D

Dosing

- Status epilepticus: Loading dose 15–20 mg/kg, maximum rate 50 mg/minute
- Seizure disorders: Initial dose of 100 mg 3 times a day titrated to target serum concentrations. Titrate dose to a therapeutic serum concentration.
- Obesity dosage adjustment: Use an adjusted body weight with a correction factor of 1.33 to account for a doubling of volume of distribution in obese patients

Pharmacokinetic Monitoring

Target serum concentration of 10–20 μg/ml total phenytoin, or free phenytoin serum concentrations of 1–2 μg/ml. Free fraction of phenytoin increases in low albumin states and CrCl < 10 ml/min.

Adverse Reactions: Most Common

Lethargy, fatigue, dizziness, blurred vision, nystagmus (an initial symptom of toxicity), cognitive impairment, gingival hyperplasia, acne, hirsutism, coarsening of facial features

Adverse Reactions: Rare/Severe/Important

Rash (Stevens-Johnson syndrome and TEN), osteomalacia (chronic administration), folate deficiency, blood dyscrasias, hepatitis, lupus-like reactions, lymphadenopathy, porphyria, arrhythmias following rapid IV administration, seizures, and coma at toxic levels, teratogenic (fetal hydantoin syndrome)

Major Drug Interactions

Drugs Affecting Phenytoin

- Antacids: Decrease bioavailability
- Carbamazepine, chronic alcohol ingestion, folic acid: Decrease phenytoin serum concentration
- Cimetidine, acute alcohol ingestion, fluconazole, valproic acid, isoniazid, and warfarin: Increase phenytoin serum concentration

Phenytoin's Effect on Other Drugs

- Phenytoin decreases serum concentrations of and may lead to the therapeutic failure of many drugs, including apixaban, carbamazepine, dabigatran, felbamate, lamotrigine, rivaroxaban, tiagabine, topiramate, valproic acid, zonisamide, folic acid, and oral contraceptives
- Phenytoin increases lithium toxicity

Essential Monitoring Parameters

Serum phenytoin levels or free phenytoin levels, liver function tests, albumin, CBC, and serum creatinine. Careful cardiac monitoring is needed during and after administering intravenous phenytoin. When administering IV loading dose, monitor HR and BP q5 min x 15 min, then q15 min until end of infusion.

Counseling Points

- Avoid alcoholic beverages
- If using oral contraceptives, consider an additional or alternative method of birth control

Key Points

- **Black Box Warning:**
  - IV phenytoin can cause hypotension. The maximum rate of IV administration is 50 mg/min
- Due to phenytoin's strong inducing influence on the CYP450 and UGT enzymatic system, be alert to any new medications added or discontinued from a patient's drug regimen because it could affect medication blood levels
- Drug interactions are complicated. Phenytoin is highly protein bound; thus, drugs that displace phenytoin from protein-binding sites increase free phenytoin levels. Monitor free phenytoin levels if displacement from protein-binding sites is suspected and clinical response is important.
- The suspension formulation of this drug interacts with tube feedings. If a patient requires tube feedings, separate dosing of the suspension formulation at least 1 to 2 hours before and 1 to 2 hours after tube feeding. Consider switching to the injection formulation if interruption of tube feeding is not feasible.
- This drug is metabolized by Michaelis-Menten pharmacokinetics. Saturation of metabolism can occur at doses used clinically, resulting in a disproportionately large increase in the serum concentration compared with a small dosage increase. When serum concentrations are subtherapeutic, increase doses cautiously.
- Serum concentration levels need to be corrected for significant renal dysfunction and/or hypoalbuminemia. Alternatively, obtain a free phenytoin level.

Pregabalin

Brand Name
Lyrica

Generic Name
Pregabalin

Rx Only
Class V controlled substance

Dosage Forms
Capsule, solution

Usage
Seizures (adjunctive therapy for partial onset), *diabetic peripheral neuropathy*, postherpetic neuralgia, *fibromyalgia*, general anxiety disorder, social anxiety disorder, hot flashes, restless leg syndrome, neuropathic pain associated with spinal cord injury

Pregnancy Category C

Dosing
- Initial dose: 50 mg three times a day or 75 mg two times a day
- Dosage adjustment: Dose can be increased to a maximum of 300 mg daily within 1 week
- Maximum dose: 600 mg daily, except for fibromyalgia, for which the maximum dose is 450 mg daily
- Renal dosage adjustment:
  - CrCl >60 ml/min: 150–600 mg daily in 2 to 3 divided doses
  - CrCl 30–60 ml/min: 75–300 mg daily in 2 to 3 divided doses
  - CrCl 15–30 ml/min: 25–150 mg daily in 1 to 2 divided doses
  - CrCl < 15 ml/min: 25–75 mg daily
- Posthemodialysis supplemental dosage: Give single additional dose of 25–150 mg.

Adverse Reactions: Most Common
Peripheral edema, increased appetite, weight gain, constipation, dry mouth, ataxia, dizziness, somnolence, euphoria, difficulty with concentrating and attention, blurred vision, diplopia

Adverse Reactions: Rare/Severe/Important
Angioedema, hypersensitivity reaction, creatine kinase elevations, thrombocytopenia, P-R interval prolongation

Essential Monitoring Parameters
Serum creatinine

Counseling Points
- Let your healthcare provider know about any muscle pain or tenderness; swelling of face or mouth; or swelling of hands, legs, or feet
- May cause drowsiness. Use caution when driving or performing tasks requiring alertness, coordination, or physical dexterity

Key Point
Use with caution in patients with Class III or IV heart failure or concomitant medications known to cause peripheral edema, due to the propensity of pregabalin to cause edema

Topiramate

Brand Name
Qudexy XR, Topamax, Topamax Sprinkle, Topiragen, Trokendi XR

Generic Name
Topiramate

Rx Only

Dosage Forms
Tablet, capsule

Usage
Seizures (monotherapy or adjunctive therapy for partial onset seizures and primary generalized tonic-clonic seizures, adjunctive treatment of seizures associated with Lennox-Gastaut syndrome), prophylaxis of migraine headache, diabetic neuropathy, cluster headache, neuropathic pain, bipolar disorder, withdrawal from alcohol, weight loss, essential tremor

Pregnancy Category D

Dosing
- Seizure disorders: Initial dose of 25–50 mg daily and increased weekly by 25–50 mg until an effective dose of 200–400 mg/day is reached in two divided doses
- Migraine prophylaxis: Initial dose of 25 mg daily and then increased weekly by 25 mg until an effective dose is reached at 50 mg twice a day
- Renal dosage adjustment: If CrCl < 70 ml/min, start at 50% the usual adult dose
- Hepatic dosage adjustment: Use with caution in patients with hepatic impairment

Adverse Reactions: Most Common
CNS (dizziness, ataxia, somnolence, psychomotor slowing, confusion, nervousness, memory impairment), loss of appetite, anorexia, taste alteration, abnormal vision, fatigue, paresthesia

Adverse Reactions: Rare/Severe/Important
Metabolic acidosis, precipitation of manic or hypomanic states in patients with bipolar disorder, oligohidrosis, hyperthermia, depression, kidney stones (concomitant use with carbonic anhydrase inhibitors should be avoided), hyperammonemia and encephalopathy, acute myopia, and secondary angle-closure glaucoma

Major Drug Interactions

Drugs Affecting Topiramate

Phenytoin, carbamazepine, and lamotrigine: Decrease serum concentrations of topiramate

Topiramate's Effect on Other Drugs

- Topiramate increases serum concentration of phenytoin and lithium
- Topiramate decreases oral contraceptive concentrations, possibly leading to failure
- Topiramate increases risk of hyperammonemia and encephalopathy in patients on valproic acid

Essential Monitoring Parameters

Serum creatinine, basic metabolic panel (to assess for metabolic acidosis)

Counseling Points

- Drink lots of fluids to prevent the formation of kidney stones
- Use caution with other CNS medications and alcohol due to increased risk of CNS side effects
- If using oral contraceptives, consider an additional or alternative method of birth control
- Tingling sensation (paresthesia) may occur and is a common side effect

Key Point

Avoid pregnancy while on topiramate. Effective contraception should be used in women who are not planning a pregnancy. Consider alternative medications in women who wish to become pregnant.

◉ Valproate Sodium

Brand Names

Depakene, Depacon, Depakote, Depakote ER, Depakote Sprinkle

Generic Names

Valproate sodium, valproic acid, and divalproex sodium (divalproex is converted to the active moiety, valproic acid, in the GI tract)

Rx Only

Dosage Forms

Tablet (immediate-, delayed-, and extended-release), capsule (immediate- and delayed-release), syrup, injection

Usage

Seizures (monotherapy and adjunctive therapy for simple and complex absence seizures, and complex partial seizures, adjunctive therapy for multiple seizure types), manic episodes associated with bipolar disorder, prophylaxis for migraine headaches, mood disorders, status epilepticus, diabetic neuropathy, postherpetic neuralgia

Pregnancy Category D (When used for migraine prophylaxis - Category X)

Dosing

- Seizure disorders:
  - Initial dose: 10–15 mg/kg per day in divided doses
  - Dosage adjustment: Titrate dose by 5–10 mg/kg per day weekly until a therapeutic response is observed or intolerable side effects
  - Maximum dose: 60 mg/kg per day
  - Extended-release formulation: Can be given once daily
  - Conversion from a stable dose of valproic acid and its derivatives to the extended-release formulation requires an 8% to 20% increase in total daily dose to maintain the same serum concentration
- Status epilepticus: IV loading dose of 20–40mg/kg
- Mania:
  - Depakote ER:
    - Initial dose: 25 mg/kg once daily
    - Dosage adjustment: Titrate to maximum of 60 mg/kg daily
- Migraine prophylaxis:
    - Initial dose: 250 mg twice a day
    - Dosage adjustment: Titrate up to 1000 mg daily
  - Depakote ER:
    - Initial dose: 500 mg daily for 7 days
    - Dosage adjustment: Titrate up to 500–1000 mg daily based on response
- Hepatic dosage adjustment: Consider dose reduction in hepatic impairment. Use is contraindicated in severe liver dysfunction.

Pharmacokinetic Monitoring

Epilepsy target serum concentration is 50–100 µg/ml, although some patients may be well controlled on concentrations outside of this range. Mania target serum concentration is 85–125 µg/ml.

Adverse Reactions: Most Common

Abdominal pain; nausea; vomiting; anorexia initially, weight gain with chronic use; drowsiness; ataxia; alopecia; blurred vision; asthenia

Adverse Reactions: Rare/Severe/Important

Hepatotoxicity (can be fatal), pancreatitis (can be fatal), teratogenic, hyperammonemia, thrombocytopenia, hypothermia, multiorgan hypersensitivity

Major Drug Interactions

Drugs Affecting Valproate/Divalproex

- Phenytoin, phenobarbital, primidone, carbamazepine, lamotrigine, rifampin, and carbapenem antibiotics : Decrease valproate serum concentration
- Cimetidine, aspirin, and felbamate: Increase valproate serum concentration

Valproate/Divalproex's Effect on Other Drugs

- Valproate increases serum concentrations of benzodiazepines, zidovudine, tricyclic antidepressants, phenobarbital, 10, 11-carbamazepine epoxide (an active metabolite of carbamazepine)

Contraindications

Patients with urea cycle disorder

Essential Monitoring Parameters

Valproic acid serum levels, liver function tests, CBC, serum ammonia levels

Counseling Point

Contact healthcare provider if nausea, vomiting, anorexia, lethargy, or jaundice occur because these may be signs of liver problems

Key Points

- **Black Box Warning:**
  - Valproic acid formulations may cause hepatotoxicity, pancreatitis, and teratogenicity
- GI side effects can be reduced by using the delayed-release formulation
- Due to their inhibitory influence on the CYP450 enzymatic system, be alert to any new medications added or discontinued from a patient's drug regimen because it could affect medication concentrations
- Consider an alternative AED in women of childbearing age due to teratogenic risk

◉ Zonisamide

Brand Name

Zonegran

Generic Name

Zonisamide

Rx Only

Dosage Form

Capsules

Usage

Adjunctive therapy for treatment of partial seizures; migraines

Pregnancy Category C

Dosing

- Initial dose: 100 mg p.o. daily titrate by 100 mg every 2 weeks until 400 mg daily
- Max dose: 600 mg. Doses above 400 mg do not appear to increase response
- Avoid use in renal impairment (CrCl < 50 ml/min)

Adverse Reactions: Most Common

Drowsiness, psychomotor slowing, kidney stones

Adverse Reactions: Rare/Severe/Important

Severe skin reactions (e.g., Stevens Johnson syndrome, toxic epidermal necrolysis [TEN]), plastic anemia, oligohidrosis, and hyperthermia

Major Drug Interactions

Drugs Affecting Zonisamide

- Phenytoin, carbamazepine, phenobarbital: Decrease zonisamide concentrations
- Valproic acid: Increase zonisamide concentrations
- Avoid concomitant use with carbonic anhydrase inhibitors (e.g., topiramate) since zonisamide also exhibits weak carbonic anhydrase inhibiting activity

Contraindications

Zonisamide is contraindicated in patients with sulfonamide allergy

Essential Monitoring Parameters

Serum creatinine and BUN

Counseling Points

- Use effective contraception while on zonisamide
- Drink plenty of water to avoid kidney stones
- Report any skin rash immediately
- Drowsiness and psychomotor slowing are the most common side effects
- For children on zonisamide, loss of normal sweating with or without a fever may occur. Contact your doctor immediately.

Key Points

- Do not use in patients with sulfonamide allergy
- Instruct patients to drink plenty of fluids to prevent kidney stones
- Monitor for changes in mood, suicidal behavior, or suicidal ideation
- Oligohidrosis and hyperthermia can occur in children, putting them at risk for heat stroke

ANTIDEPRESSANTS, MISCELLANEOUS

Introduction

This group of antidepressants encompasses some first-line agents, especially in the presence of compelling indications. Their agents may have fewer sexual side effects than the more commonly used selective serotonin reuptake inhibitors (SSRIs).

Mechanism of Action for the Drug Class

These agents have multiple mechanisms of action, including blocking the presynaptic reuptake of serotonin and/or norepinephrine, thereby increasing concentrations of these CNS neurotransmitters in the synapse. Bupropion is also a weak inhibitor of dopamine reuptake. Mirtazapine has central presynaptic alpha-2 adrenergic antagonism, which leads to increased release of serotonin and norepinephrine.

Counseling Points for the Drug Class

- All antidepressants require several weeks of continuous use before symptoms improve. Patients should be cautioned that some side effects will probably occur before the therapeutic effect.
- The most important aspect of treating depression is that therapy must continue for 6 to 9 months after improvement. Stopping the drug therapy too soon greatly increases the risk of the depression returning.

Key Points for the Drug Class

- **Black Box Warning:**
  - All antidepressants have a warning that they increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18 to 24 years of age) with major depressive disorder (MDD) and other psychiatric disorders
- Monitoring parameters for all antidepressants should include suicide ideation (especially at the beginning of therapy or when doses are changed), mental status for efficacy, and the most common side effects of the individual agent. Side-effect monitoring is especially important because side effects can occur before therapeutic effects and negatively impact adherence.
- All antidepressants are contraindicated with the concomitant use of monoamine oxidase inhibitors (MAOIs) or sibutramine and use within 14 days of MAOI therapy

Members of the Drug Class

In this section: Bupropion, mirtazapine, trazodone. Others: nefazodone

◉ Bupropion

Brand Names

Wellbutrin, Wellbutrin-SR, Wellbutrin XL, Zyban, Budeprion

Generic Name

Bupropion

Rx Only

Dosage Forms

Tablet, sustained-release tablet, extended-release tablet

Usage

Major depressive disorder, smoking cessation

Pregnancy Category C

Dosing

- Depression:
  - Immediate-release: Start with 100 mg twice daily and increase to the 300 mg target dose by day 4
  - Sustained- or extended-release: Start with 150 mg once daily in the morning. Increase to the 300 mg target dose by day 4.
- Smoking cessation: Start with 150 mg daily for 3 days, then increase to 150 mg twice daily. Continue treatment for 7 to 12 weeks.
- Renal dosage adjustment: Start with reduced dosage or dosing frequency and monitor carefully
- Hepatic dosage adjustment: Start with reduced dosage or dosing frequency and monitor carefully

Adverse Reactions: Most Common

Headache, insomnia, xerostomia, weight loss, agitation, tachycardia

Adverse Reactions: Rare/Severe/Important

Seizures

Major Drug Interactions

Major substrate of CYP2B6, strong inhibitor of CYP2D6

Drugs Affecting Bupropion

- CYP2B6 inhibitors: Increase concentrations
- CYP2B6 inducers: Decrease concentrations

Bupropion's Effect on Other Drugs

- Alcohol: Increases seizure risk
- Herbs used for depression and anxiety (e.g., kava kava, St. John's wort): Increases CNS depression
- CYP2D6 substrates: Increases concentrations

Contraindications

Seizure disorder, history of anorexia/bulimia

Counseling Points

- Patients should be aware that bupropion is marketed under the brand names Wellbutrin and Zyban. These are the same medication; they should not be taken together.

- Avoid alcohol because it can increase the risk for seizures. Excessive use or abrupt discontinuation of alcohol or sedatives can also increase seizure risk.
- Dry mouth and insomnia are common and may improve over time. If insomnia occurs, recommend taking the first dose as early as possible. The patient may also take the second dose 8 hours after the first.

Key Points

- **Black Box Warning:**
  - Neuropsychiatric effects have been observed when bupropion is used in smoking cessation
- Bupropion is particularly useful for patients suffering sexual side effects or excessive sedation from other agents
- Start elderly patients at half the usual initial doses

Mirtazapine

Brand Names

Remeron, Remeron Sol Tabs

Generic Name

Mirtazapine

Rx Only

Dosage Forms

Tablet, orally disintegrating tablet (ODT)

Usage

Major depressive disorder

Pregnancy Category C

Dosing

- Initial dose: 15 mg daily at bedtime, increased to 30–45 mg daily
- Maximum dose: 45 mg daily
- Renal dosage adjustment: No specific recommendations are given. Start with reduced dosage and monitor carefully.
- Hepatic dosage adjustment: No specific recommendations are given. Start with reduced dosage and monitor carefully.

Adverse Reactions: Most Common

Somnolence, xerostomia, increased appetite, weight gain, increase cholesterol, constipation

Major Drug Interactions

Major substrate of CYP1A2, CYP2D6, and CYP3A4

Counseling Points

- Sedation is most common with lower doses of mirtazapine; it is best to take before bedtime when starting therapy
- Weight gain and changes in cholesterol can occur
- SolTab is formulated to dissolve on the tongue without water

Key Points

- Paradoxically, higher doses (30–45 mg) may be less sedating than the initial 15 mg dose
- Mirtazapine may cause fewer sexual side effects compared with the SSRIs
- Start elderly patients at half the usual initial dose
- Due to its effects on sleep and weight, mirtazapine is a good choice for patients with depression characterized by insomnia and loss of appetite

Trazodone

Brand Names

Desyrel, Oleptro

Generic Name

Trazodone

Rx Only

Dosage Forms

Tablet, extended-release tablet

Usage

Major depressive disorder, insomnia

Pregnancy Category C

Dosing

- Depression:
  - Initial dose: 150 mg daily divided into 2 to 3 doses
  - Dosage adjustment: Increase to 300–500 mg daily as a target dose for depression
  - Maximum dose:
    - Tablets: 600 mg daily
    - Extended-release tablets: 375 mg daily
- At bedtime for nighttime sedation:
  - Initial dose: 25–50 mg
  - Usual dose: 100-150 mg
  - Maximum dose: 200 mg

Adverse Reactions: Most Common

Sedation, orthostatic hypotension, dizziness, headache

Adverse Reactions: Rare/Severe/Important

Priapism

Major Drug Interactions

Major substrate of CYP3A4

Drugs Affecting Trazodone

CYP3A4 inhibitors (e.g., sibutramine, venlafaxine, protease inhibitors, some SSRIs): Increase concentrations

Trazodone's Effect on Other Drugs

Alcohol and other CNS depressants: Increases effects

Counseling Points

- Risk of sedation is high, use caution when performing tasks that require mental alertness
- Immediate-release formulations should be taken after meals
- Extended-release tablets should be taken on an empty stomach. Do not crush or chew the tablet.

Key Points

- Trazodone is most often used as a hypnotic due to its sedative properties or prescribed as an adjunctive therapy for depression. If dual therapy with another serotonergic agent is recommended, patients should be thoroughly educated on the signs and symptoms of serotonin syndrome and be seen immediately if such symptoms occur.
- Nefazodone is a similar agent that is rarely used due to a high incidence of liver failure. Trazodone does not carry this risk.

ANTIDEPRESSANTS, SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

Introduction

This small class of antidepressants has fewer sexual side effects compared with selective serotonin reuptake inhibitors (SSRIs) and a patient-friendly adverse-effect profile. Like SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs) are first-line treatments for depression and anxiety. Duloxetine and venlafaxine are also used for the management of certain pain syndromes.

Mechanism of Action for the Drug Class

These medications work in depression by blocking the neuronal reuptake of serotonin and norepinephrine. It is their action on norepinephrine that is responsible for their efficacy in neuropathic pain syndromes, as well as their toxicity profile of GI upset and increased blood pressure.

Counseling Points for the Drug Class

- All antidepressants require several weeks of continuous use before symptoms improve. Patients should be cautioned that some side effects will probably occur before the therapeutic effect.
- The most important aspect of treating depression is that therapy must continue for 6 to 9 months after the patient has shown improvement. Stopping the drug therapy too soon greatly increases the risk of relapse.
- Patients should be counseled on the signs and symptoms of serotonin toxicity, especially if on more than one medication that increases serotonin concentrations due to the increased risk of serotonin syndrome. Such symptoms include agitation, restlessness, diaphoresis, tachycardia, hyperthermia, nausea, vomiting, and loss of coordination.
- Avoid alcohol and maintain adequate hydration unless otherwise restricted
- Counsel patients on the black box warning and to be seen immediately or go to their local ER if symptoms of suicide ideation occur. Also, counsel patients to report any sudden changes in mental status.

Key Points for the Drug Class

- **Black Box Warning:**
  - Antidepressants may increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18 to 24 years of age) with major depressive disorder (MDD) and other psychiatric disorders
- Monitoring parameters for all antidepressants should include suicide ideation (especially at the beginning of therapy or when doses are changed), mental status for efficacy, and the most common side effects of the individual agent. Side-effect monitoring is especially important because side effects can occur before therapeutic effects and negatively impact adherence.
- For all SNRIs, blood pressure should be monitored at baseline and periodically thereafter, with extra caution in uncontrolled hypertensive patients. Liver and kidney function should also be monitored and doses adjusted accordingly.
- All antidepressants are contraindicated with the concomitant use of MAOIs or sibutramine and use within 14 days of MAOI therapy
- Concomitant use of multiple agents that increase serotonin, such as SSRIs, SNRIs, and TCAs, should be avoided due to the risk for serotonin syndrome, a serious and potentially life-threatening reaction. If this combination is used, patients should be educated on the signs and symptoms of serotonin toxicity (see previous discussion). Other medications that can increase the risk for serotonin syndrome

when used with antidepressants include triptans, linezolid, dextromethorphan, meperidine, and OTC treatments for depression, such as 5-HTP, SAMe, and St. John's wort.

Members of the Drug Class

In this section: Duloxetine, venlafaxine
Others: Desvenlafaxine, milnacipran

◉ Duloxetine

Brand Name

Cymbalta

Generic Name

Duloxetine

Rx Only

Dosage Form

Delayed-release capsule

Usage

Major depressive disorder; *generalized anxiety disorder (GAD)*; *pain syndromes associated with diabetic neuropathy, fibromyalgia, and chronic musculoskeletal pain*

Pregnancy Category C

Dosing

- Initial dose: 40–60 mg daily in 1 or 2 divided doses
- Maximum dose: 120 mg daily
- Note: Doses > 60 mg daily have not been shown to be more effective
- Renal dosage adjustment: Avoid in patients with CrCl < 30 ml/min
- Hepatic dosage adjustment: Avoid in patients with hepatic impairment

Adverse Reactions: Most Common

Nausea, headache, somnolence, dry mouth, insomnia, other GI complaints

Adverse Reactions: Rare/Severe/Important

SIADH, serotonin syndrome

Major Drug Interactions

- Major substrate of CYP1A2 and CYP2D6
- Moderate inhibitor of CYP2D6

Drugs Affecting Duloxetine

CYP2D6 and CYP1A2 inhibitors (paroxetine, fluvoxamine): Increase effects

Duloxetine's Effect on Other Drugs

Alcohol and other CNS depressants, thioridazine, beta-agonists: Increases effects

Contraindication

Uncontrolled, narrow-angle glaucoma

Counseling Points

- Swallow capsule whole. Do not crush or chew.
- Monitor glucose closely in diabetic patients

Key Points

- May take 2 to 3 weeks to be effective. Doses may need to be titrated upward.
- Drug should be tapered off over a 2-week period when discontinuing therapy
- May be confused with fluoxetine (Prozac)

◉ Venlafaxine

Brand Names

Effexor, Effexor XR

Generic Name

Venlafaxine

Rx Only

Dosage Forms

Tablet, extended-release tablet, extended-release capsule

Usage

Major depressive disorder, generalized anxiety disorder (GAD), seasonal affective disorder (SAD), diabetic neuropathy, panic disorder, hot flashes, obsessive compulsive disorder (OCD), ADHD, migraine prophylaxis

Pregnancy Category C

Dosing

- Initial dose for most indications: 75 mg daily that should be increased to 150 mg by days 4 to 7
- Target dose range: 150–225 mg daily (can divide dose for immediate-release tablets)
- Maximum dose:
  - Immediate-release: 375 mg daily
  - Extended-release: 225 mg daily
- Renal dosage adjustment: Reduce by 25% to 50% in patients with CrCl 10–70 ml/min
- Hepatic dosage adjustment: Reduce by 50% in mild to moderate impairment

Adverse Reactions: Most Common

Headache, insomnia, nervousness, somnolence, GI complaints, increased diastolic blood pressure, dizziness, sexual dysfunction

Adverse Reactions: Rare/Severe/Important

SIADH, serotonin syndrome

Major Drug Interactions

Major substrate of CYP3A4 and CYP2D6

Drugs Affecting Venlafaxine

CYP2D6 and CYP3A4 inhibitors: Increase effects

Venlafaxine's Effect on Other Drugs

CNS depressants, trazodone: Increases effects

Counseling Points

- Take with food to decrease GI upset
- Extended-release capsules should be swallowed whole; do not crush or chew. Alternatively, contents may be emptied onto a spoonful of applesauce and swallowed without chewing.

Key Points

- Dosing should be tapered down over a 2-week period when discontinuing therapy
- Not FDA approved for use in children
- Start elderly patients at half the usual initial dose

ANTIDEPRESSANTS, SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Introduction

When the selective serotonin reuptake inhibitors (SSRIs) came to the market in the late 1980s, this class of antidepressants replaced the tricyclic antidepressants (TCAs) as first-line treatment for depression. Compared with TCAs, SSRIs have a much safer and more favorable side-effect profile. These agents are among the most widely prescribed medications in the United States. They are used for major depressive disorder (MDD) and various anxiety disorders, and their use for nonpsychiatric disorders is increasing.

Mechanism of Action for the Drug Class

SSRIs block presynaptic reuptake of serotonin, thereby increasing the concentration of this CNS neurotransmitter in the synapse

Counseling Points for the Drug Class

- All antidepressants require several weeks of continuous use before symptoms improve. Patients should be cautioned that some side effects will probably occur before the therapeutic effect.
- The most important aspect of treating depression may be that therapy must continue for 6 to 9 months after improvement. Stopping drug therapy too soon greatly increases the risk of depression returning.
- All SSRIs may cause somnolence or insomnia. Each patient's response should determine if once-daily dosing is in the morning or afternoon.
- Patients should be counseled on the signs and symptoms of serotonin toxicity, especially if on more than one medication that increases serotonin concentrations, due to the increased risk of serotonin syndrome. Such symptoms include agitation, restlessness, diaphoresis, tachycardia, hyperthermia, nausea, vomiting, and loss of coordination.
- Avoid alcohol and maintain adequate hydration, unless otherwise restricted
- Counsel on the black box warning and seek immediate medical care if symptoms of suicide ideation occur. Also, counsel patients to report any sudden changes in mental status.

Key Points for the Drug Class

- **Black Box Warning:**
  - Antidepressants may increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18 to 24 years of age) with major depressive disorder (MDD) and other psychiatric disorders
- Monitoring parameters for all antidepressants should include suicide ideation (especially at the beginning of therapy or when doses are changed), mental status for efficacy, and the most common side effects of the individual agent. Side-effect monitoring is especially important because side effects can occur before therapeutic effects and negatively impact adherence.
- All antidepressants are contraindicated with the concomitant use of monoamine oxidase inhibitors (MAOIs) or sibutramine and use within 14 days of MAOI therapy
- Concomitant use of multiple agents that increase serotonin, such as SSRIs, SNRIs, and TCAs, should be avoided due to the risk for serotonin syndrome, a serious and potentially life-threatening reaction. If this combination is utilized, patients should be educated on the signs and symptoms of serotonin toxicity (see earlier discussion). Other medications that can increase the risk for serotonin syndrome when used with antidepressants include triptans, linezolid, dextromethorphan, meperidine, and OTC treatments for depression, such as 5-HTP, SAMe, and St. John's wort.

Members of the Drug Class

In this section: Citalopram, escitalopram oxalate, fluoxetine, paroxetine, sertraline, vortioxetine, vilazodone.
Others: Fluvoxamine, vilazodone

◉ Citalopram

Brand Name

Celexa

Generic Name

Citalopram

Rx Only

Dosage Forms
Tablet, oral solution

Usage
Major depressive disorder, obsessive compulsive disorder (OCD)

Pregnancy Category C

Dosing
- Initial dose: 20 mg daily, increased in 1 to 2 weeks to 40 mg daily if little or no response
- Maximum dose:
  - Due to the risk for dose-related QT-interval prolongation, the recommended maximum dose is 40 mg daily
  - In patients > 60 years of age, poor metabolizers of CYP2C19, or patients on concurrent moderate-to-strong CYP2C19 inhibitors such as cimetidine: 20 mg daily
- Renal dosage adjustment: Use with caution in patients with CrCl < 20 ml/min
- Hepatic dosage adjustment: Do not exceed 20 mg in patients with hepatic impairment

Adverse Reactions: Most Common
Nausea, loss of appetite; somnolence or insomnia, sexual dysfunction, headache, xerostomia, diaphoresis

Adverse Reactions: Rare/Severe/Important
Hyponatremia, SIADH, QT-interval prolongation

Major Drug Interactions
- Major substrate of CYP2C19 and CYP3A4
- Contraindicated with pimozide

Drugs Affecting Citalopram
- Strong CYP2D6, CYP2C19, CYP3A4 inhibitors, including quinidine, some protease inhibitors, ticlopidine: Increase levels
- Carbamazepine and other strong CYP inducers: Decrease levels

Citalopram's Effect on Other Drugs

CNS depressants, buspirone, clozapine: Increases effect

Contraindications
Previously, use in patients with conditions known to have a risk of QT prolongation was contraindicated; however, those who require treatment with citalopram (i.e., no other alternative) may derive benefit from a low dose, such as 20 mg as long as diligent ECG monitoring is employed

Counseling Point
Start elderly patients at half the usual initial doses

Key Point
Drug should be tapered off over a 2-week period when discontinuing therapy

◉ Escitalopram Oxalate

Brand Name
Lexapro

Generic Name
Escitalopram oxalate

Rx Only

Dosage Forms
Tablet, oral solution

Usage
Major depressive disorder, generalized anxiety disorder (GAD)

Pregnancy Category C

Dosing
- Initial dose: 10 mg daily, which may be increased to 20 mg after 1 to 2 weeks
- Maximum dose: 20 mg daily
- Hepatic dosage adjustment:
  - Mild to moderate hepatic impairment:
    - Initial dose: 5 mg
    - Maximum dose: 10 mg
  - Severe hepatic impairment: Has not been studied, no recommendations available (use with caution)

Adverse Reactions: Most Common
Nausea, loss of appetite, somnolence or insomnia, headache, sexual dysfunction

Adverse Reactions: Rare/Severe/Important
Hyponatremia, SIADH

Major Drug Interactions
- Major substrate of CYP2C19 and CYP3A4
- Contraindicated with pimozide

Drugs Affecting Escitalopram
- Strong CYP2D6, CYP2C19, CYP3A4 inhibitors including quinidine, some protease inhibitors, ticlopidine: Increase effects
- Serotonin agonists (e.g., "triptans"): May result in serotonin syndrome

Escitalopram's Effect on Other Drugs
- CNS depressants, buspirone, clozapine: Increases effects

Counseling Point
Start elderly patients at half the usual initial doses

Key Points

- Drug should be tapered off over a 2-week period when discontinuing therapy
- This drug is the S-enantiomer of citalopram and may not have advantages over citalopram. The dosing ratio between the two is 1:2 (i.e., 10 mg of escitalopram is equal to 20 mg of citalopram).

Fluoxetine

Brand Names

Prozac, Prozac Weekly, Sarafem

Generic Name

Fluoxetine

Rx Only

Dosage Forms

Capsule, tablet, delayed-release capsule for weekly dosing, oral solution

Usage

Major depressive disorder, *obsessive compulsive disorder (OCD)*; bulimia nervosa; premenstrual dysphoric disorder (PMDD); panic disorder with or without agoraphobia, in combination with olanzapine for treatment-resistant or bipolar I depression

Pregnancy Category C

Dosing

- Initial dose: 10–20 mg daily
- Dosage adjustments: Adjustments may be made every 2 weeks to a maximum dose of 80 mg daily
- OCD and bulimia nervosa: Often require the high end of the dosage range
- Treatment-resistant depression and bipolar I disorder: A combination product with olanzapine is available called Symbyax. Initial dosing is 6–25mg daily titrated to maximum dose of 12–50 mg daily.
- Renal dosage adjustment: Use lower doses and monitor closely in patients with severe renal disease
- Hepatic dosage adjustment: Use lower doses and monitor closely in patients with severe hepatic disease

Adverse Reactions: Most Common

Nausea, loss of appetite, xerostomia, insomnia, sexual dysfunction, headache, anxiety, nervousness (CNS stimulation)

Adverse Reactions: Rare/Severe/Important

SIADH, serotonin syndrome

Major Drug Interactions

- Major substrate for CYP2C9 and CYP2D6
- Strong inhibitor of CYP2D6, moderate inhibitor of CYP2C19 and CYP1A2
- Contraindicated with thioridazine and ziprasidone. Do not start these medications until 5 weeks after the discontinuation of fluoxetine.

Drugs Affecting Fluoxetine

- Carbamazepine: Decrease levels
- CYP2C9 and CYP2D6 inhibitors: Increase levels

Fluoxetine's Effect on Other Drugs

Alcohol, phenytoin, clozapine, tramadol, and others metabolized by CYP2D6, CYP1A2, and CYP2C19: Increases levels

Counseling Points

- Fluoxetine should always be taken in the morning to avoid insomnia. It is the most stimulating of the SSRIs.
- Do not crush, chew, or break Prozac Weekly capsules

Key Points

- Appetite suppression is common, and the drug is sometimes used for obesity
- The parent molecule and active metabolite, norfluoxetine, have a very long half-life. Therefore, steady-state concentrations may not be reached for weeks, and the drug may remain in the body for weeks after discontinuation.
- Use cautiously and at reduced dosages in elderly patients (because of its long half-life), if at all
- This medication is approved for use in children aged 7 years and older

Paroxetine

Brand Names

Paxil, Paxil CR, Pexeva

Generic Name

Paroxetine

Rx Only

Dosage Forms

Tablet, controlled-release tablet, extended-release tablet, oral suspension

Usage

Major depressive disorder, *obsessive compulsive disorder (OCD)*, panic disorder with or without agoraphobia, seasonal affective disorder (SAD), *generalized anxiety disorder (GAD)*, *posttraumatic stress disorder*, premenstrual dysphoric disorder (PMDD)

Pregnancy Category D

Dosing

- Initial dose: 10–20 mg daily
- Dosage adjustment: May increase by 10 mg every 1 to 2 weeks
- Maximum dose: 60 mg daily
- Paxil CR:
  - Initial dose: 25 mg daily
  - Maximum dose: 62.5 mg daily
- OCD and panic disorder: Higher doses may be necessary
- Renal dosage adjustment: If CrCl < 30 ml/min:
  - Immediate-release:
    - Initial dose: 10 mg daily
    - Maximum dose: 40 mg daily
  - Paxil CR:
    - Initial dose: 12.5 mg daily
    - Maximum dose: 50 mg daily
- Hepatic dosage adjustment: Severe impairment:
  - Immediate-release:
    - Initial dose: 10 mg daily
    - Maximum dose: 40 mg daily
  - Paxil CR:
    - Initial dose: 12.5 mg daily
    - Maximum dose: 50 mg daily

Adverse Reactions: Most Common

Nausea, loss of appetite, somnolence or insomnia, headache, sexual dysfunction

Adverse Reactions: Rare/Severe/Important

SIADH, serotonin syndrome

Major Drug Interactions

- Major substrate of CYP2D6
- Strong inhibitor of CYP2D6, moderate inhibitor of CYP2B6
- Contraindicated with tamoxifen and thioridazine

Drugs Affecting Paroxetine

- Buspirone, cimetidine, tramadol: Increase levels
- Carbamazepine: Decreases levels

Paroxetine's Effect on Other Drugs

- Strong inhibitor of CYP2D6 and moderate inhibitor of CYP2B6
- CNS depressants, beta blockers, carbamazepine, buspirone: Increases levels

Counseling Points

- Take in the morning to avoid insomnia
- Do not crush, chew, or break the controlled-release formulation

Key Points

- This medication should be tapered over several weeks for discontinuation
- Paroxetine causes more sexual dysfunction and anticholinergic side effects than other SSRIs
- Paroxetine has the most drug interactions of all of the SSRIs
- Use this agent cautiously and at reduced dosages in elderly patients
- There is no real advantage to the controlled-release formulation

Sertraline

Brand Name

Zoloft

Generic Name

Sertraline

Rx Only

Dosage Forms

Tablet, solution

Usage

Major depressive disorder, *obsessive compulsive disorder (OCD)*, *panic disorder, posttraumatic stress disorder (PTSD)*, seasonal affective disorder (SAD), generalized anxiety disorder (GAD), eating disorders

Pregnancy Category C

Dosing

- Initial dose: 25–50 mg daily, which is usually increased to an effective range of 100–200 mg daily
- Hepatic dosage adjustment: Use cautiously in patients with hepatic impairment due to extensive hepatic metabolism of this agent

Adverse Reactions: Most Common

Nausea, diarrhea, loss of appetite, somnolence or insomnia, headache, sexual dysfunction, dizziness, fatigue, xerostomia, tremors, diaphoresis

Adverse Reactions: Rare/Severe/Important

SIADH, serotonin syndrome

Major Drug Interactions

- Major substrate of CYP2D6 and a minor substrate of many others
- Moderate inhibitor of CYP2B6, CYP2C19, CYP2D6, and CYP3A4
- Contraindicated with thioridazine, pimozide, and disulfiram

Drugs Affecting Sertraline

Strong CYP2D6 inhibitors: Increase effects

Sertraline's Effect on Other Drugs

Carbamazepine, phenytoin, CNS depressants, clozapine, risperidone: May increase effects

Key Points

- There are fewer clinically significant drug interactions with this agent compared with other SSRIs when used at lower doses, although these doses are often subtherapeutic (50–100 mg daily)

- On average, initial doses must be increased for full therapeutic effect, probably more so than with other SSRIs
- Start elderly patients at half the usual initial doses

Vortioxetine

Brand Name
Trintellix

Generic Name
Vortioxetine

Rx Only

Dosage Form
Tablet

Usage
Major Depressive Disorder

Pregnancy Category C

Dosing
- Initial dose: 10 mg daily, increase to 20 mg daily as tolerated
- CYP2D6 poor metabolizers: Maximum dose is 10 mg daily
- Concomitant therapy with strong CYP2D6 inhibitors: Reduce total daily dose by half when strong inhibitors are coadministered
- Concomitant therapy with strong CYP2D6 inducers: When coadministered together for greater than 14 days, consider increasing the daily dose. Do not exceed three times the original dose.
- Hepatic dosage adjustment: In severe impairment, use is not recommended

Adverse Reactions: Most Common
Nausea, diarrhea, sexual dysfunction, dizziness, xerostomia

Adverse Reactions: Rare/Severe/Important
Seizure, SIADH, serotonin syndrome

Major Drug Interactions
- Major substrate of CYP2D6
- Contraindicated with MAO inhibitors
- When switching from vortioxetine to a MAO inhibitor, allow 21 days to elapse before initiating therapy

Drugs Affecting Vortioxetine
- Strong CYP2D6 inhibitors: Increase effects
- Strong CYP2D6 inducers: Decrease effects

Vortioxetine's Effect on Other Drugs
- May increase effects of carbamazepine, apixaban, rivaroxaban, edoxaban, and NSAIDS

Key Point
Use with caution in patients with a history of seizure disorder or with conditions predisposing to seizures

Vilazodone

Brand Name
Viibryd

Generic Name
Vilazodone

Rx Only

Dosage Form
Tablet

Usage
Major depressive disorder

Pregnancy Considerations
The teratogenicity and long-term effects of vilazodone use during pregnancy are not known. The risks and benefits of therapy should be weighed.

Dosing
- Initial dose: 10 mg once daily, increase to 20 mg daily on day 8, if well tolerated. May increase to 40 mg daily on day 15, depending on response and tolerability. Take with food.
- Hepatic dosage adjustment: No dose adjustment necessary

Adverse Reactions: Most Common
Nausea, diarrhea, headache, sexual dysfunction, dizziness, drowsiness, xerostomia

Adverse Reactions: Rare/Severe/Important
SIADH, serotonin syndrome

Major Drug Interactions
Contraindicated with MAO inhibitors

Drugs Affecting Vilazodone
Strong CYP2D6 inhibitors: Increase effects

Vilazodone's Effect on Other Drugs
Antiplatelets and anticoagulants: may increase bleeding risk

Key Point
Vilazodone's concentration is decreased when taken on an empty stomach. Take with food.

ANTIDEPRESSANTS, TRICYCLICS

Introduction

The tricyclic antidepressants (TCAs) are one of the oldest groups of antidepressant agents. Because of their many adverse effects, particularly their anticholinergic and sedative properties as well as the introduction of safer agents such as the SSRIs, these medications are not frequently used for depression, nor are they considered first-line therapy. The possibility of death from overdose is another drawback with these agents. These drugs are more commonly used for the treatment of chronic nerve pain conditions at lower doses than to treat depression. They still have a role in treatment-resistant depression (i.e., after therapeutic failure with several first-line agents).

Mechanism of Action for the Drug Class

TCAs block presynaptic reuptake of serotonin and norepinephrine, thereby increasing concentrations of these CNS neurotransmitters in the synapse. It is their action on norepinephrine that is responsible for their efficacy in neuropathic pain conditions.

Counseling Points for the Drug Class

- All antidepressants require several weeks of continuous use before symptoms improve. Patients should be cautioned that some side effects will probably occur before the therapeutic effect.
- The most important aspect of treating depression may be that therapy must continue for 6 to 9 months after improvement. Stopping drug therapy too soon greatly increases the risk of the depression returning.
- Patients should be counseled on the signs and symptoms of serotonin toxicity, especially if on more than one medication that increases serotonin concentrations due to the increased risk of serotonin syndrome. Such symptoms include agitation, restlessness, diaphoresis, tachycardia, hyperthermia, nausea, vomiting, and loss of coordination.
- Orthostatic hypotension is possible with these agents. Advise patients to take a full minute at the side of the bed before getting up in the morning.
- Sedation decreases with continued treatment
- Recommend sugarless drinks, candies, and gum for dry mouth. More water is the easiest and most convenient "therapy" for dry mouth and to prevent constipation.
- Avoid alcohol and maintain adequate hydration unless otherwise restricted
- Counsel patients on the black box warning and to be seen immediately or go to their local ER if symptoms of suicide ideation occur. Also, counsel patients to report any sudden changes in mental status.

Key Points for the Drug Class

- **Black Box Warning:**
  - Antidepressants may increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18 to 24 years of age) with major depressive disorder (MDD) and other psychiatric disorders
- Monitoring parameters for all antidepressants should include suicide ideation (especially at the beginning of therapy or when doses are changed), mental status for efficacy, and the most common side effects of the individual agent. Side-effect monitoring is especially important because side effects can occur before therapeutic effects and negatively impact adherence.
- All antidepressants are contraindicated with the concomitant use of monoamine oxidase inhibitors (MAOIs) or sibutramine and use within 14 days of MAOI therapy
- Concomitant use of multiple agents that increase serotonin, such as SSRIs, SNRIs, and TCAs, should be avoided due to the risk for serotonin syndrome, a serious and potentially life-threatening reaction. If this combination is used, patients should be educated on the signs and symptoms of serotonin toxicity (see previous discussion). Other medications that can increase the risk for serotonin syndrome when used with antidepressants include triptans, linezolid, dextromethorphan, meperidine, and OTC treatments for depression, such as 5-HTP, SAMe, and St. John's wort.

Members of the Drug Class

In this section: Amitriptyline, doxepin, nortriptyline
Others: Amoxapine, clomipramine, desipramine, imipramine, protriptyline, trimipramine

◉ Amitriptyline

Brand Name

Elavil

Generic Name

Amitriptyline

Rx Only

Dosage Forms

Tablet, injection

Usage

Depression, neuropathic pain syndromes, migraine prophylaxis

Pregnancy Category C

Dosing

- Initial dose: 10–25 mg at bedtime
- Dosage adjustment: To prevent severe side effects, the dose should be increased gradually. Adjustments should be made every 2 to 3 days at 10–25 mg

increments. It may take weeks to get a response after leveling off at approximately 150 mg daily. The dose may need to be increased gradually to 200 mg or more.
- Maximum dose: 300 mg daily
- Renal dosage adjustment: No specific dose adjustment recommended. Use with caution and monitor plasma levels and patient response.
- Hepatic dosage adjustment: No specific dose adjustment recommended. Use with caution and monitor plasma levels and patient response.

Pharmacokinetic Monitoring
Therapeutic levels: 100–250 ng/ml

Adverse Reactions: Most Common
Anticholinergic effects (dry mouth, constipation, urinary hesitancy, blurred vision), orthostatic hypotension, sedation (tolerance to these effects is common)

Adverse Reactions: Rare/Severe/Important
AV conduction changes, heart block, myocardial infarction

Major Drug Interactions
- Major substrate of CYP2D6
- Contraindicated with thioridazine, ziprasidone, and cisapride

Drugs Affecting Amitriptyline
- CYP2D6 inhibitors (e.g., quinidine, protease inhibitors, SSRIs, valproic acid, cimetidine, tramadol): Increase effects
- Carbamazepine, barbiturates, rifamycins: Decrease effects

Amitriptyline's Effect on Other Drugs
- CNS depressants, anticholinergic drugs, alpha-1 agonists, quinidine, tramadol, thioridazine, and antiarrhythmics: Increases effects

Contraindication
Acute recovery phase post myocardial infarction

Essential Monitoring Parameters
ECG in older adults and patients with cardiac disease, blood pressure, and pulse rate prior to and during initial therapy. Amitriptyline is one of the few antidepressants where blood concentrations are sometimes monitored, although not in most clinical practices because they do not always correlate with clinical effectiveness. Therapeutic levels of amitriptyline and its active metabolite, nortriptyline, should be in the range of 100–250 ng/ml and 50–150 ng/ml, respectively. Toxicity can be seen at concentrations > 500 ng/ml.

Key Points
- Start elderly patients at half the usual initial doses
- Monitor glucose closely in diabetic patients because this medication can cause hyperglycemia
- Amitriptyline, a tertiary TCA, is metabolized to the active metabolite nortriptyline, a secondary TCA that is marketed as a separate agent. Compared with tertiary TCAs, secondary TCAs have a slightly more favorable side-effect profile (e.g., fewer anticholinergic effects).

Doxepin

Brand Names
Sinequan, Prudoxin, Zonalon, Silenor, Adapin

Generic Name
Doxepin

Rx Only

Dosage Forms
Capsule, tablet, cream, oral solution

Usage
Depression, insomnia characterized by difficulty with sleep maintenance, pruritic skin conditions (topical cream)

Pregnancy Category C

Dosing
- Initial dose: 25–50 mg at bedtime
- Dosage adjustment: Dose may be increased very gradually to 150–300 mg over 2 to 3 weeks
- Maximum dose: A single dose should not exceed 150 mg
- Silenor (insomnia):
  - 3–6 mg once daily 30 minutes prior to bedtime
  - Maximum dose: 6 mg daily
- Topical cream: Apply as a thin film four times daily
- Hepatic dosage adjustment: Use a lower dose and adjust gradually in hepatic impairment

Adverse Reactions: Most Common (Oral)
Anticholinergic effects (dry mouth, constipation, urinary hesitancy, blurred vision), orthostatic hypotension, sedation

Adverse Reactions: Rare/Severe/Important (Oral)
AV conduction changes, heart block, myocardial infarction

Major Drug Interactions
- Major substrate of CYP2D6
- Contraindicated with thioridazine and ziprasidone

Drugs Affecting Doxepin
- CYP2D6 inhibitors (e.g., quinidine, protease inhibitors, SSRIs, valproic acid, tramadol): Increase effects
- Carbamazepine: Decreases effects

Doxepin's Effect on Other Drugs
- CNS depressants, anticholinergic drugs, alpha-1 agonists, quinidine, tramadol: Increases effects

Contraindications

Narrow-angle glaucoma, urinary retention

Key Points

- Administration should be limited to bedtime to make use of its sedative effects
- Elderly are patients more prone to experiencing the "hangover effect." Start elderly patients at half the usual initial dose.

Nortriptyline

Brand Names

Pamelor, Aventyl

Generic Name

Nortriptyline

Rx Only

Dosage Forms

Capsule, solution

Usage

Depression

Pregnancy Category Not Defined

Dosing

- Initial dose: 25–50 mg daily
- Dosage adjustment: Increase slowly to a maximum dose of 150 mg daily
- Hepatic dosage adjustment: Use lower doses with slower titration in hepatic impairment

Pharmacokinetic Monitoring

Therapeutic levels of nortriptyline should be in the range of 50–150 ng/ml. Toxicity can be seen with levels > 500 ng/ml.

Adverse Reactions: Most Common

Anticholinergic effects (dry mouth, constipation, urinary hesitancy, blurred vision), orthostatic hypotension, sedation. These effects are less than that of the parent compound, amitriptyline.

Adverse Reactions: Rare/Severe/Important

AV conduction changes, heart block, myocardial infarction

Major Drug Interactions

- Major substrate of CYP2D6
- Contraindicated with thioridazine and ziprasidone

Drugs Affecting Nortriptyline

- CYP2D6 inhibitors (e.g., quinidine, protease inhibitors, SSRIs, valproic acid, tramadol): Increase effects
- Carbamazepine: Decreases effects

Nortriptyline's Effect on Other Drugs

- CNS depressants, anticholinergic drugs, alpha-1 agonists, quinidine, tramadol: Increases effects

Contraindication

Acute recovery phase postmyocardial infarction

Essential Monitoring Parameters

ECGs in older adults and patients with cardiac disease; blood pressure and pulse rate prior to and during initial therapy; weight. Nortriptyline is one of the few antidepressants where blood level data are sometimes used, although in the average clinical practice, levels are not commonly drawn because they do not always correlate with clinical efficacy.

Key Points

- Nortriptyline, a secondary TCA, is the active metabolite of amitriptyline
- It has a slightly more favorable side-effect profile compared with amitriptyline, especially with regard to sedation
- Like amitriptyline, nortriptyline is also used sometimes in the treatment of chronic pain syndromes
- Start elderly patients at half the usual initial dose

ANTIMANIC AGENTS, MOOD STABILIZERS

Introduction

This class of psychiatric agents is essentially made up of lithium and valproic acid (and its congeners). Valproic acid is covered in the section on anticonvulsant agents. These drugs are mainstays in the acute and maintenance therapy of the bipolar disorders.

Mechanism of Action for Lithium

Lithium produces multiple effects on CNS neurotransmitters via altered cation transport across cell membranes, which influences the reuptake of serotonin and/or norepinephrine

Members of the Drug Class

In this section: Lithium carbonate
Others: Valproic acid

Lithium Carbonate

Brand Names

Eskalith, Eskalith CR, Lithobid

Generic Names

Lithium carbonate, lithium citrate (liquid formulations)

Rx Only

Dosage Forms

Capsule, tablet, extended-release capsule, extended-release tablet, oral solution

Usage

Bipolar disorder, mania, augmenting agent for refractory depression

Pregnancy Category D

Dosing

- Initial dose:
  - 600–1200 mg daily (in 2–3 divided doses)
  - Extended-release: 900–1800 mg daily in 2 doses
- Dosage adjustments are made based on serum levels
- Renal dosage adjustment:
  - CrCl 10–50 ml/min: Administer 50% to 75% of dose
  - CrCl < 10 ml/min: Administer 25% to 50% of dose
  - Severe renal impairment: Should not be used

Pharmacokinetic Monitoring

Trough levels should be drawn 8 to 12 hours after the previous dose. Levels for acute mania (0.6–1.2 mEq/l) are slightly higher than maintenance levels (0.5–0.9 mEq/l). Levels should be drawn twice weekly until levels and clinical status are stable, then every 1 to 3 months thereafter.

Adverse Reactions: Most Common

GI complaints, dizziness, polydipsia, tremor, sedation, leucocytosis

Adverse Reactions: Rare/Severe/Important

Hypothyroidism, arrhythmias

Major Drug Interactions

Drugs Affecting Lithium

- Diuretics, NSAIDs, tetracyclines, angiotensin receptor antagonists: Decrease excretion of lithium, increasing lithium levels
- High sodium intake: Increases excretion of lithium, decreasing lithium levels

Lithium's Effect on Other Drugs

- MAOIs: Possibility of severe CNS reactions
- CNS neurotoxicity has been rarely reported when lithium is added to some antipsychotic agents, SSRIs, TCAs, and phenytoin

Contraindications

Severe cardiovascular or renal disease, severe debilitation, dehydration, sodium depletion, pregnancy

Essential Monitoring Parameters

Lithium levels, renal, thyroid, and cardiovascular function, fluid status, serum electrolytes, CBC with differential, urinalysis, pregnancy test for nonsterile females, symptoms of toxicity (GI complaints, tremors, confusion, somnolence, seizures)

Counseling Points

- Drug concentration monitoring is frequently performed
- Do not crush or chew extended-release products
- Maintain adequate hydration unless otherwise restricted
- Avoid changes in sodium content because reduction in sodium can increase lithium toxicity
- Inform your healthcare provider before taking new medications, including OTC products, because many can interact with lithium
- Decreased appetite, altered taste, drowsiness, and dizziness may occur, especially early in therapy. Immediately report unresolved diarrhea, abrupt changes in weight, muscular tremors, lack of coordination, fever, or changes in urinary volume.

Key Points

- **Black Box Warning**:
  - Lithium levels predict toxicity and should be monitored
- Lithium is one of the first-line treatments for bipolar disorders
- Lithium is contraindicated in severe renal or cardiac disease and in pregnancy
- After long-term use, hypothyroidism may develop in up to 10% of patients
- Lithium is not metabolized. It is excreted through the kidneys unchanged. Monitoring renal function and electrolytes throughout therapy is prudent.
- Lithium will be reabsorbed when extra sodium is excreted due to diuretic therapy, heavy perspiration, etc.
- Diuretics, ACE inhibitors, and NSAIDs increase lithium concentrations. Use with caution or decrease lithium dose and monitor concentrations.

ANTIPSYCHOTIC AGENTS, ATYPICAL

Introduction

Atypical agents have replaced the older, typical antipsychotics, such as haloperidol, as first-line treatment of psychotic disorders, especially for chronic management in the outpatient setting. Compared with typical agents, atypicals have fewer side effects, including extrapyramidal symptoms (EPS), a collection of drug-induced movement disorders, and hyperprolactinemia. The incidence of other adverse effects, such as anticholinergic effects, may also be somewhat lower. The tradeoff is that atypicals can cause significant weight gain, hyperlipidemia, and increased glucose, which can lead to diabetes mellitus. Some of the agents are approved as adjunctive treatments for depression.

Mechanism of Action for the Drug Class

There agents have effects on multiple CNS neurotransmitter systems. Dopamine inhibition (D_1, D_2, and D_4 receptors) and serotonin antagonism (5-HT_2), along with unknown effects on glutamate and GABA, lead to the therapeutic effects in the treatment of schizophrenia and other psychotic states.

Counseling Points for the Drug Class

- When appropriate, suggest to patients that they speak to their prescriber about taking their entire daily dose at bedtime
- Patients must not use alcohol or other CNS depressants. Patients also should avoid drugs of abuse because they will worsen symptoms.
- Advise caution with driving and operating heavy machinery, especially for the more sedating agents
- Patients should use caution in hot weather due to the potential for thermoregulatory changes. Maintain adequate hydration unless otherwise restricted.
- Diabetic patients need to closely monitor blood glucose and report any changes
- Report changes in weight and psychiatric status
- Immediately report chest pain, palpitations, persistent GI effects, tremors, altered gait, changes in vision, fever, and hyperpyrexia, especially when associated with muscle rigidity and altered mental status (signs of neuroleptic malignant syndrome [NMS], a rare but severe and life-threatening condition)
- The risks of extrapyramidal reactions should be explained. Patients should be told to report abnormal involuntary body movements or abnormal muscle contractions. If there is an acute problem, they should contact their physician immediately or go to the emergency department of their local hospital.
- If a dose is missed, do not double the dose. Resume the regular schedule the following day.
- When possible, explain to patients that their illness is a biologic problem, which should be treated like any other medical diagnosis requiring treatment
- Do not stop the medication or stop regular visits to a healthcare provider

Key Points for the Drug Class

- **Black Box Warning:**
  - Patients with dementia-related behavioral disorders treated with atypical antipsychotics are at an increased risk of death compared with placebo
- Metabolic complications should be monitored with all atypical antipsychotic agents. Monitor weight prior to treatment, at 4 weeks, 8 weeks, 12 weeks, and then quarterly. Monitor waist circumference, BMI, and vital signs. Consider switching agents if there is a 5% or greater increase in weight from baseline. Monitor fasting lipids and glucose/Hgb A1c prior to treatment, at 3 months, and then annually.
- Monitor for EPS with use of the abnormal involuntary movement scale (AIMS)

Members of the Drug Class

In this section: Aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone
Others: Clozapine, paliperidone, asenapine, lurasidone

◉ Aripiprazole

Brand Names

Abilify, Abilify Discmelt

Generic Name

Aripiprazole

Rx Only

Dosage Forms

Tablet, oral dissolving tablet (ODT), oral solution, injection solution

Usage

Schizophrenia, bipolar disorder, augmenting agent in treatment of major depressive disorder (MDD), agitation associated with schizophrenia or bipolar I disorder (injection).

Pregnancy Category C

Dosing

- Initial dose: 10–15 mg daily, which may be increased over a few weeks to a maximum of 30 mg daily
- Bipolar disorder: Acute treatment may use higher doses
- Depression: Lower doses used as adjunct to treatment
- Renal dosage adjustment: No dosage adjustments are needed

- Hepatic dosage adjustment: No dosage adjustments are needed

Adverse Effects: Most Common

Agitation, insomnia, headache, extrapyramidal effects (dose related)

Adverse Effects: Rare/Severe/Important

NMS, hyperglycemia, drug-induced diabetes mellitus

Major Drug Interactions

Major substrate of CYP2D6 and CYP3A4

Drugs Affecting Aripiprazole

- Inhibitors of CYP450, such as fluoxetine, paroxetine, quinidine, azole antifungals, and clarithromycin: Increase effects
- Inducers of CYP450, such as carbamazepine, phenobarbital, and phenytoin: Decrease effects

Aripiprazole's Effect on Other Drugs

- CNS depressants: Additive effects

Counseling Point

Take at the same time each day without regard to meals

Key Point

This agent may cause minimal or less weight gain compared with other atypical agents. It is often preferred for this reason.

Olanzapine

Brand Names

Zyprexa, Zyprexa IntraMuscular, Zyprexa Zydis, Zyprexa Relprevv

Generic Name

Olanzapine

Rx Only

Dosage Forms

Tablet, oral dissolving tablet (ODT), short-acting IM injection, long-acting IM injection

Usage

Schizophrenia, bipolar disorder, in combination with fluoxetine for treatment-resistant or bipolar I depression, psychosis/agitation associated with Alzheimer's disease

Pregnancy Category C

Dosing

- Initial dose: 5–10 mg daily
- Dosage adjustment: May be increased by 5 mg daily at weekly intervals to 15–20 mg daily
- Maximum dose: 20 mg daily
- Hepatic dosage adjustment: No specific dosing recommendations are given for hepatic impairment, although adjustment may be necessary

Adverse Reactions: Most Common

Somnolence, headache, weight gain, and glucose and lipid abnormalities

Adverse Reactions: Rare/Severe/Important

NMS, hyperglycemia, drug-induced diabetes mellitus, extrapyramidal effects (dose related)

Major Drug Interactions

Major substrate of CYP1A2

Drugs Affecting Olanzapine

- CYP1A2 inhibitors (e.g., fluvoxamine, ketoconazole, others): Increase levels
- CYP inducers (e.g., rifampin, carbamazepine, omeprazole): Decrease levels

Olanzapine's Effect on Other Drugs

- CNS depressants: Increases effects

Counseling Points

- Olanzapine frequently causes drowsiness. These effects are more common at the beginning of therapy.
- Remove the ODT from the foil blister by peeling back the foil. Do not push the tablet through the foil. Place tablet in mouth immediately upon removal. Tablet dissolves rapidly in saliva and may be swallowed with or without liquid.
- Olanzapine comes coformulated with fluoxetine (Symbyax)

Key Points

- **Black Box Warning:**
  - Zyprexa Relprevv (injection) can lead to sedation (including coma) and delirium (including agitation, anxiety, confusion, and disorientation) following the use of this product. Caution is required.
- Of the atypicals, olanzapine is one of the worst at causing weight gain and metabolic complications

Quetiapine

Brand Names

Seroquel, Seroquel XR

Generic Name

Quetiapine

Rx Only

Dosage Forms

Tablet, extended-release tablet

Usage

Schizophrenia, bipolar disorder, bipolar depression, adjunctive treatment of depression

Pregnancy Category C

Dosing

- Initial dose: 25–50 once or twice daily
- Dosage adjustment: Dose may be increased by 50–100 mg daily every few days to usual target dose of 400–500 mg daily
- Maximum dose: 800 mg daily
- Hepatic dosage adjustment: Caution in hepatic impairment. Use smaller dose increases (25–50 mg daily).

Adverse Reactions: Most Common

Somnolence, headache, sedation, weight gain, lipid, and glucose abnormalities

Adverse Reactions: Rare/Severe/Important

Neuroleptic malignant syndrome, hyperglycemia, drug-induced diabetes mellitus, extrapyramidal effects

Major Drug Interactions

Major substrate of CYP3A4

Drugs Affecting Quetiapine

- Strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, phenobarbital): Decrease levels
- CYP3A4 inhibitors (e.g., azole antifungals, protease inhibitors): Increase levels

Quetiapine's Effect on Other Drugs

- CNS depressants: Increases effects

Counseling Points

- Extended-release capsules should be swallowed whole and not split, chewed, or crushed. Take the medication without food or with a light meal.
- This agent will cause drowsiness. These effects are more common at the beginning of therapy.

Key Points

- The risk for extrapyramidal effects are lower with quetiapine compared with other atypical agents
- This agent is used in lower doses (12.5–50 mg) to treat acute ICU delirium

◉ Risperidone

Brand Names

Risperdal, Risperdal Consta, Risperdal M-tab

Generic Name

Risperidone

Rx Only

Dosage Forms

Tablet, solution, oral dissolving tablet (ODT), extended-release injection

Usage

Schizophrenia, bipolar disorder, treatment of irritability or aggression in autism, Tourette's syndrome

Pregnancy Category C

Dosing

- Initial dose: 2 mg daily in 1 to 2 divided doses
- Dosage adjustment: Increase dose every 1 to 2 days to target dose of 4–8 mg daily
- Renal dosage adjustment: Initial doses should be halved in patients with renal impairment
- Hepatic dosage adjustment: Initial doses should be halved in patients with hepatic impairment
- Careful monitoring is required for continued therapy

Adverse Reactions: Most Common

Somnolence, headache, sedation, weight gain, lipid abnormalities, extrapyramidal side effects (dose dependent)

Adverse Reactions: Rare/Severe/Important

Neuroleptic malignant syndrome, hyperglycemia, drug-induced diabetes mellitus

Major Drug Interactions

Major substrate for CYP2D6

Drugs Affecting Risperidone

- Carbamazepine and other CYP inducers: Decrease levels
- CYP2D6 inhibitors, such as paroxetine, quinidine, and some protease inhibitors: Increase levels

Risperidone's Effect on Other Drugs

- CNS depressants: Increases effects

Counseling Point

Risperidone may cause drowsiness. This effect is more common at the beginning of therapy.

Key Points

- The orthostatic hypotensive effects of this agent are due to alpha-adrenergic blockade and are most commonly seen at initiation of therapy
- Of the atypicals, risperidone has the highest incidence of extrapyramidal symptoms, particularly at doses > 6 mg daily

◉ Ziprasidone

Brand Name

Geodon

Generic Name

Ziprasidone

Rx Only

Dosage Forms

Capsule, injection

Usage

Schizophrenia, bipolar disorder, acute agitation in patients with schizophrenia (injection)

Pregnancy Category C

Dosing

- Initial oral: 20–40 mg twice daily that can be rapidly increased to target dose of 80 mg twice daily. It should be given with morning and evening meals because administration on an empty stomach reduces absorption by ~40%.
- IM dosing for acute agitation: 10–20 mg/dose up to 40 mg daily. Oral therapy should replace continual IM injections.
- Renal dosage adjustment: No dosage recommendations for renal impairment. The IM formulation should be used with caution in renal impairment because it contains cyclodextrin, an excipient that is renally cleared.
- Hepatic dosage adjustment: No dosage recommendations for hepatic impairment

Adverse Reactions: Most Common

Headache, somnolence, extrapyramidal side effects

Adverse Reactions: Rare/Severe/Important

QT-prolongation, NMS, hyperglycemia, drug-induced diabetes mellitus

Major Drug Interactions

Minor substrate of CYP3A4 and CYP1A2

Drugs Affecting Ziprasidone

- Azole antifungals and ciprofloxacin: Increase effects

Ziprasidone's Effect on Other Drugs

- CNS depressants: Increases effects
- Use with caution with drugs that prolong the QTc interval because additive prolongation can occur

Contraindications

History of or current prolonged QT, congenital long QT syndrome, recent myocardial infarction, uncompensated heart failure, concurrent use of other QT-prolonging agents, such as class Ia or class III antiarrhythmics

Counseling Points

- Drowsiness can occur and is more common at the beginning of therapy
- This agent must be taken with food to be properly absorbed

Key Point

This drug is usually used as a long-term agent and must be taken with food to be effective. The IM formulation is also used acutely in the inpatient setting.

ANTIPSYCHOTIC AGENTS, TYPICAL

Introduction

The first-generation antipsychotic agents, sometimes called "typical" antipsychotic agents, were the first class of medications used to treat schizophrenia and related psychoses. The newer atypical agents have essentially replaced their use in chronic management, although typical agents, such as haloperidol, are still widely used in the inpatient setting to treat acute psychoses. Typical antipsychotics have a high incidence of hyperprolactinemia, QTc-prolongation, and extrapyramidal symptoms (EPS), a collection of drug-induced movement disorders that can have a profound negative impact on daily functioning and quality of life. One type of EPS, tardive dyskinesia, is irreversible and untreatable.

Mechanism of Action for the Drug Class

Agents block postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors, improving positive symptoms associated with schizophrenia and other psychotic states. Dopamine blockade in other areas of the brain is responsible for typical antipsychotic toxicity, including EPS, and increases in serum prolactin.

Counseling Points for the Drug Class

- Patients must not use alcohol or other CNS depressants. Patients should also avoid drugs of abuse because they can worsen symptoms.
- Patients should use caution in hot weather due to the potential for thermoregulatory changes. Maintain adequate hydration unless restricted.
- Diabetic patients need to closely monitor blood glucose and report any changes
- Report changes in weight and psychiatric status
- Immediately report chest pain, palpitations, persistent GI effects, tremors, altered gait, changes in vision or mental status, fever, and hyperpyrexia, especially when associated with muscle rigidity and altered mental status (signs of neuroleptic malignant syndrome [NMS], a rare but severe and life-threatening condition)
- The risks of extrapyramidal reactions should be explained. Patients should be told to report abnormal

involuntary body movements or abnormal muscle contractions. If there is an acute problem, they should contact their physician immediately or go to the emergency department of their local hospital.
- If a dose is missed, do not double the dose. Resume the regular schedule the following day.
- Do not stop the medication or stop regular visits to healthcare providers

Key Points for the Drug Class

- **Black Box Warning:**
  - Patients with dementia-related behavioral disorders treated with antipsychotics are at an increased risk of death compared with placebo
- Monitor for EPS with use of the abnormal involuntary movement scale (AIMS)

Members of the Drug Class

In this section: Haloperidol
Others: Chlorpromazine, fluphenazine, loxapine, molindone, perphenazine, thioridazine, thiothixene, trifluoperazine

◉ Haloperidol

Brand Names

Haldol, Haldol Decanoate

Generic Name

Haloperidol

Rx Only

Dosage Forms

Tablet, oral solution, short-acting injection solution (as lactate), long-acting injection (as decanoate)

Usage

Schizophrenia, ICU delirium, OCD, Tourette disorder

Pregnancy Category C

Dosing

- Psychoses:
  - Oral:
    - Initial dose: 0.5–5 mg two to 3 times daily
    - Maximum dose: 30 mg daily
  - IM
    - As lactate: 2–5 mg every 4 to 8 hours, as needed
    - As decanoate: Must establish oral dose before changing to IM decanoate. Initial: 10 to 20 times the daily oral dose given at 4-week intervals (maintenance dose: 10 to 15 times initial oral dose)
- Note: QTc prolongation may occur with cumulative doses ≥ 35 mg, and torsade de pointes has been reported with single doses of ≥ 20 mg

Pharmacokinetic Monitoring

Therapeutic levels for psychotic disorders: 5–20 ng/ml (less for Tourette's syndrome and mania). Toxicity is associated with levels > 42 ng/ml. Note that levels are rarely drawn in clinical practice.

Adverse Reactions: Most Common

Agitation, insomnia, headache, akathisia, and other extrapyramidal effects

Adverse Reactions: Rare/Severe/Important

NMS, severe EPS, cardiac changes, such as QT prolongation

Major Drug Interactions

- Major substrate of CYP2D6 and CYP3A4
- Moderate inhibitor of CYP2D6 and CYP3A4

Drugs Affecting Haloperidol

- CYP2D6 and CYP3A4 inhibitors: Increase levels
- CYP2D6 and CYP3A4 inducers (e.g., rifampin): Decrease levels

Haloperidol's Effect on Other Drugs

- CNS depressants: Additive effects

Contraindications

Parkinson's disease, severe CNS depression, coma

Essential Monitoring Parameters

Vital signs, lipids, glucose, BMI, ECG with off-label IV administration, EPS, serum concentrations

Counseling Points

- The IM formulation may take 2 to 3 weeks to achieve desired results
- Dilute oral concentration with juice or water
- Avoid skin contact with medication because it may cause contact dermatitis

Key Points

- For the most part, chronic management of psychotic disorders has been replaced by the atypical agents due to their lesser incidence of EPS, although some patients will still be on typical agents long term
- EPS is an important side effect of typical antipsychotics. Patients should be counseled on the signs and symptoms of EPS and to report to their local ER immediately if such symptoms occur. EPS monitoring using the AIMS should be employed throughout therapy.
- If haloperidol is to be used for acute delirium, the lowest effective dose should be used due to its risk for QT prolongation, which can lead to *torsades de pointes*.

CHOLINESTERASE INHIBITORS

Introduction

Donepezil and rivastigmine are reversible inhibitors of acetylcholinesterase used for the treatment of mild-to-moderate Alzheimer's disease (AD). The rationale for use of these agents in AD is to increase CNS acetylcholine concentrations, which can be deficient in patients with AD.

Mechanism of Action for the Drug Class

The therapeutic effects from donepezil and rivastigmine in AD is primarily due to an increase in the concentration of acetylcholine through the reversible inhibition of hydrolysis by acetylcholinesterase. Donepezil, a piperidine derivative, is a centrally active, reversible inhibitor of acetylcholinesterase and is structurally unrelated to other anticholinesterase agents (i.e., tacrine, physostigmine). Rivastigmine, a carbamate derivative, is an intermediate-acting, reversible acetylcholinesterase inhibitor that is structurally related to physostigmine but is unrelated to donepezil or tacrine.

Members of the Drug Class

In this section: Donepezil, rivastigmine
Others: Galantamine, tacrine

⦿ Donepezil

Brand Names

Aricept, Aricept ODT

Generic Name

Donepezil

Rx Only

Dosage Forms

Film-coated tablet, orally disintegrating tablet (ODT)

Usage

Treatment of mild, moderate, or severe dementia of the Alzheimer's type, behavioral syndromes in dementia, mild to moderate dementia associated with Parkinson's disease, Lewy body dementia

Pregnancy Category C

Dosing

Alzheimer's disease:

- Mild to moderate: 5 mg daily at bedtime; may increase to 10 mg daily at bedtime after 4 to 6 weeks
- Moderate to severe: 5 mg daily at bedtime; may increase to 10 mg daily at bedtime after 4 to 6 weeks; may further increase to 23 mg daily after ≥ 3 months

Adverse Reactions: Most Common

Nausea, vomiting, diarrhea, bradycardia, hypertension, dizziness, headache, insomnia, fatigue

Adverse Reactions: Rare/Severe/Important

Atrioventricular block, torsades de pointes, GI hemorrhage

Major Drug Interactions

Drugs Affecting Donepezil

- Cholinergic agents: Additive cholinergic side effects
- Anticholinergic agents, St. John's wort: Decrease effect
- Gingko biloba: Increases adverse effects/toxicity

Donepezil's Effect on Other Drugs

- Nondepolarizing neuromuscular-blocking agents: Exaggerated muscle relaxation

Counseling Points

- Administer at bedtime without regard to food
- Allow ODT tablet to dissolve completely on tongue and follow with water
- Donepezil is not a cure, but it may help reduce symptoms of Alzheimer's disease
- Improvement associated with donepezil therapy is not maintained following discontinuance of the drug. Contact prescriber before discontinuing medication.
- Report severe nausea, vomiting, diarrhea, anorexia, dehydration, weight loss, insomnia, or signs/symptoms of GI bleeding, especially with current NSAID use
- GI upset is usually transient and occurs at dose titration

Key Points

- Effects will vary from patient to patient but may be observed as subtle improvement in cognition, function, or behavior over time
- Benefits associated with donepezil therapy are not maintained following discontinuance of the drug, suggesting that the underlying disease process of dementia is not altered by this medication
- GI upset generally resolves in 1 to 3 weeks

⦿ Rivastigmine

Brand Name

Exelon

Generic Names

Rivastigmine (transdermal patch), rivastigmine tartrate (oral)

Rx Only

Dosage Forms

Capsule, solution, transdermal patch

Usage

Treatment of mild-to-moderate dementia associated with Alzheimer's or Parkinson's disease, severe dementia associated with Alzheimer's disease, Lewy body dementia

Pregnancy Category B

Dosing

- Mild to moderate dementia associated with Alzheimer's disease:
  - Oral:
    - Initial dose: 1.5 mg twice daily with meals
    - Dosage adjustment: If tolerated, increase dose every 2 weeks by 1.5 mg twice daily
    - Maximum dose: 6 mg twice daily
  - Transdermal:
    - Initial: 4.6 mg/24-hour patch once daily
    - Dosage adjustment: After a minimum of 4 weeks and good tolerability, increase to 9.5 mg/24-hour patch once daily
- Mild-to-moderate dementia associated with Parkinson's disease:
  - Oral:
    - Initial dose: 1.5 mg twice daily with meals
    - Dosage adjustment: If tolerated, increase dose by 1.5 mg/dose up to 6 mg twice daily, with a minimum of 4 weeks at each dose
  - Transdermal:
    - Initial: 4.6 mg/24-hour patch once daily
    - Dosage adjustment: After a minimum of 4 weeks and good tolerability, increase to 9.5 mg/24-hour patch once daily
- Conversion from oral therapy:
  - Oral daily dose < 6 mg: Switch to 4.6 mg/24-hour patch. Apply patch on the next day following last oral dose.
  - Oral daily dose 6–12 mg: Switch to 9.5 mg/24-hour patch. Apply patch on the next day following last oral dose.
- Renal dosage adjustment: No dosage adjustment necessary; titrate to tolerability
- Hepatic dosage adjustment: No dosage adjustment necessary; titrate to tolerability
- Low body weight (< 50 kg): Use particular caution when titrating above the recommended dose of 9.5 mg/24 hour

Adverse Reactions: Most Common

Diarrhea, nausea, vomiting, weight loss, indigestion, dizziness, loss of appetite, skin irritation

Adverse Reactions: Rare/Severe/Important

Cardiac arrest, supraventricular tachycardia, tachyarrhythmia, GI hemorrhage, bronchospasm

Major Drug Interactions

Drugs Affecting Rivastigmine

- Gingko biloba: Increases effect
- Cholinergic agents: Additive cholinergic effects
- Anticholinergic agents, dipyridamole, nicotine (increased rivastigmine clearance): Decrease effect

Rivastigmine's Effect on Other Drugs

- Nondepolarizing neuromuscular-blocking agents: Exaggerated muscle relaxation
- Antipsychotics: Neurotoxicity
- Beta blockers: bradycardia
- Corticosteroids: Muscle weakness

Contraindications

Other carbamate derivatives (neostigmine, pyridostigmine, physostigmine)

Counseling Points

- Administration in the morning and evening with food is recommended because the incidence of adverse GI effects may be related to high peak plasma concentrations
- Antiemetics may be used to control GI symptoms
- The oral solution and capsules may be interchanged at equal doses; the oral solution should be administered using the oral dosing syringe according to the patient instructions provided by the manufacturer
- The capsule should be swallowed whole; do not crush or chew. The oral solution can be swallowed directly from the syringe or mixed with water, soda, or cold fruit juice. Stir well and drink within 4 hours of mixing.
- The transdermal system is applied topically to a dry, hairless area of intact skin. Remove and discard the protective liner and firmly press the patch with the adhesive side touching the skin. Placement on the back is recommended to reduce the risk of removal by the patient, but the upper arm or chest may be used as well.
- The transdermal system is worn continuously for 24 hours. Rotate application site. Do not apply to the same site within 14 days. Remove existing patch prior to applying new patch. Store patches in a cool, dry place; avoid exposure to heat sources.
- Report persistent abdominal discomfort, diarrhea, or constipation; significantly increased salivation, sweating, tearing, or urination; chest pain or palpitations; acute headache; CNS changes, increased muscle, joint, or body pain; vision changes or blurred vision; shortness of breath, coughing, or wheezing; skin rash

Key Points

- Titrate to target doses based on GI tolerability; adverse GI effects can be severe at higher than recommended doses
- Advise against sudden discontinuation of drug. Patients who miss doses for several days in a row should contact a healthcare professional, as the drug may need to be restarted at a lower dose.

ANTI-PARKINSON'S AGENTS, DOPAMINE AGONISTS

Introduction

These pharmacologically dissimilar agents affect dopamine receptors. Carbidopa/levodopa is a combination product used primarily for the treatment of Parkinson's disease (PD). Ropinirole hydrochloride is a nonergoline dopamine agonist that has a higher specificity to D_3 subtypes of dopamine receptors. Normal motor function depends on the synthesis and release of dopamine by neurons projecting from the substantia nigra to the corpus striatum. The progressive degeneration of these neurons that occurs in PD disrupts this pathway and results in decreased levels of dopamine. Striatal dopamine levels in symptomatic PD are decreased by 60% to 80%.

Mechanism of Action for the Drug Class

Levodopa circulates in the plasma to the blood–brain barrier (BBB), where it crosses and is converted to dopamine in the CNS; carbidopa inhibits peripheral decarboxylation of levodopa, decreasing the conversion to dopamine in peripheral tissues. This results in higher plasma levels of levodopa available to enter the CNS. The proposed mechanism of action of ropinirole is due to stimulation of postsynaptic dopamine D_2-type receptors within the caudate putamen in the brain. Ropinirole also has moderate in vitro affinity for opioid receptors.

Adverse Reactions for the Drug Class: Most Common

Loss of appetite, nausea, vomiting, constipation, abdominal pain, dizziness, headache, fatigue

Adverse Reactions for the Drug Class: Rare/Severe/Important

Heart disease, orthostatic hypotension, dose-related dyskinesia, somnolence, hallucinations, psychotic disorders, neuroleptic malignant syndrome

Counseling Points for the Drug Class

- Take exactly as directed; do not change dosage or discontinue without consulting the prescriber. Do not crush sustained-release formulations.
- Take with meals if GI upset occurs, before meals if dry mouth occurs, and after eating if drooling or nausea occur
- Do not use alcohol and prescription/OTC sedatives or CNS depressants without consulting prescriber. Urine or perspiration may appear darker.
- Use caution when driving, climbing stairs, or engaging in tasks requiring alertness
- Use caution when rising from sitting or lying position
- Report exacerbation of underlying depression or psychosis
- Report unresolved constipation or vomiting, CNS changes, increased muscle spasticity or rigidity, unusual skin changes, or significant worsening of condition

Members of the Drug Class

In this section: Carbidopa/levodopa, ropinirole
Others: Amantadine, apomorphine, bromocriptine, entacapone, pramipexole, rotigotine

Carbidopa/Levodopa

Brand Names

Sinemet, Sinemet CR, Parcopa (orally disintegrating tablet)

Generic Name

Carbidopa/levodopa

Rx Only

Dosage Forms

Immediate-release tablet, sustained-release tablet, orally disintegrating tablet (ODT)

Usage

Idiopathic Parkinson's disease, postencephalitic parkinsonism, symptomatic parkinsonism from carbon monoxide and/or manganese intoxication, restless leg syndrome, amblyopia

Pregnancy Category C

Dosing

- Parkinson's disease:
  - Immediate-release tablet:
    - Initial: Carbidopa 25 mg/levodopa 100 mg three times a day titrated to desired effects. Use of more than one dosage strength or dosing four times a day may be required.
    - Maximum dose: 8 tablets of any strength per day or 200 mg carbidopa and 2000 mg levodopa
  - Sustained-release tablet:
    - Initial: Carbidopa 50 mg/levodopa 200 mg 2 times a day, at intervals not < 6 hours
    - Dosage adjustment: May adjust every 3 days; intervals should be between 4 and 8 hours during the waking day
    - Maximum dose: 8 tablets per day
- Renal dosage adjustment: Use with caution; no specific dosing recommendation in manufacturer labeling
- Hepatic dosage adjustment: Use with caution; no specific dosing recommendation in manufacturer labeling

Major Drug Interactions

Drugs Affecting Carbidopa/Levodopa

- Nonselective MAOIs (phenelzine, tranylcypromine): Increase effect

- Antipsychotics, iron salts, metoclopramide, phenytoin, pyridoxine: Decrease effect
- Herbal considerations: Avoid kava kava

Contraindications

Narrow-angle glaucoma, history of melanoma, nonselective MAOI use concurrently or < 2 weeks prior, suspicious and undiagnosed skin lesions

Counseling Point

When administering the ODT, use dry hands to gently remove the tablet from the bottle and immediately place tablet on top of tongue and swallow with saliva after it dissolves. Administration with a liquid is not necessary.

Key Points

- Therapeutic effects may take several weeks or months to achieve and frequent monitoring may be needed during first weeks of therapy
- Do not use MAOIs concurrently or within 2 weeks of carbidopa/levodopa
- Patients using concomitant antihypertensives may be at an increased risk for orthostatic hypotension
- Avoid high-protein diets and high doses (> 200 mg daily) of vitamin B_6 (pyridoxine)
- False-positive or false-negative urinary glucose results may occur with certain testing agents; false-positive urine ketone results may occur with certain testing agents

◉ Ropinirole

Brand Names

Requip, Requip XL

Generic Name

Ropinirole

Rx Only

Dosage Forms

Immediate-release tablet, extended-release tablet

Usage

Idiopathic Parkinson's disease, early Parkinson's disease not receiving concomitant levodopa therapy, advanced Parkinson's disease on concomitant levodopa therapy, moderate-to-severe primary restless leg syndrome

Pregnancy Category C

Dosing

- Parkinson's disease:
  - Immediate-release tablets:
    - Initial dose: 0.25 mg 3 times daily
    - Dosage adjustment: Titrate weekly to therapeutic response in an ascending dose schedule from the initial dose to a maximum dose of 24 mg daily in divided doses
    - Discontinuation taper: Should be gradually tapered over 7 days
  - Extended-release tablets:
    - Initial dose: 2 mg once daily orally
    - Dosage adjustment: Titrate at a weekly or longer interval to therapeutic response at 2 mg daily increments to a maximum dose of 24 mg daily
    - Discontinuation taper: Gradually taper over 7 days
- Restless leg syndrome:
  - Initial dose: 0.25 mg once daily
  - Dosage adjustment: Titrate as needed to a maximum of 4 mg
  - All doses are once daily 1 to 3 hours before bedtime; doses should be titrated weekly when appropriate, based on clinical response and efficacy
  - Doses up to 4 mg per day may be discontinued without tapering
- Renal dosage adjustment: Use with caution in cases of severe renal impairment (CrCl < 30 ml/min); has not been studied in this population
- Hepatic dosage adjustment: Titrate with caution; has not been studied in this population

Major Drug Interactions

Drugs Affecting Ropinirole

- Ciprofloxacin, CYP1A2 inhibitors, estrogen derivatives, MAOIs: Increase effect
- Antipsychotics, CYP1A2 inducers, metoclopramide: Decrease effect
- Herbal considerations: Avoid kava kava, gotu kola, valerian, St. John's wort

Ropinirole's Effect on Other Drugs

Warfarin: May enhance the anticoagulant effect

Key Points

- Titrate dosing to achieve desired clinical response
- If therapy with a potent inhibitor of CYP1A2 is stopped or started during treatment with ropinirole, adjustment of ropinirole dose may be required
- May switch directly from immediate-release ropinirole; start an extended-release dose that matches most closely with the total daily immediate-release dose

N-METHYL-D-ASPARTATE RECEPTOR ANTAGONISTS

Introduction

Glutamate is an excitatory amino acid present in the CNS. It is thought to contribute to the pathogenesis of Alzheimer's disease by overstimulating glutamate receptors, leading to excitotoxicity and neuronal cell death. Memantine blocks the NMDA type of glutamate receptor, and during excessive receptor activation can affect magnesium and calcium ion influx and efflux. Memantine does not appear to affect normal neurotransmission but is most effective as a receptor blocker under conditions of excessive stimulation.

Mechanism of Action for the Drug Class

Memantine hydrochloride is a low to moderate affinity, noncompetitive NMDA receptor agonist that binds to NMDA receptor–operated cation channels. Memantine also blocks the 5-hydroxytryptamine-3 receptor and nicotinic acetylcholine receptors at various potencies.

Members of the Drug Class

In this section: Memantine

◉ Memantine

Brand Names

Namenda, Namenda XR

Generic Name

Memantine

Rx Only

Dosage Forms

Film-coated tablet, oral solution

Usage

Palliative treatment of moderate to severe dementia of the Alzheimer's type, mild-to-moderate vascular dementia

Pregnancy Category B

Dosing

- Immediate-release:
  - Initial: 5 mg once daily
  - Increase dose by 5 mg daily to a target dose of 20 mg daily
- Wait ≥ 1 week between dosing changes
- Doses > 5 mg daily should be given in 2 divided doses
- Titration schedule: 5 mg daily for ≥ 1 week; 5 mg twice daily for ≥ 1 week; 15 mg daily given in 5 mg and 10 mg separated doses for ≥ 1 week; then 10 mg twice daily
- Memantine tablets and oral solution are equivalent on a mg-per-mg basis
- Renal dosage adjustment:
  - Mild-to-moderate impairment: If CrCl 30–80 ml/min, no adjustment needed
  - Severe impairment: If CrCl 5–29 ml/min, then 5 mg twice daily
- Hepatic dosage adjustment: None needed for mild-to-moderate hepatic impairment

Adverse Reactions: Most Common

Dizziness, confusion, headache, diarrhea, constipation, vomiting, hypertension, back pain, cough, hallucination, somnolence, dyspnea, fatigue

Adverse Reactions: Rare/Severe/Important

Stevens-Johnson syndrome, deep-vein thrombosis (DVT), hepatitis, liver failure, cerebral vascular accident (CVA), seizure, transient ischemic attack (TIA), acute renal failure, neuroleptic malignant syndrome

Major Drug Interactions

Drugs Affecting Memantine

- Alkalinizing agents (carbonic anhydrase inhibitors, sodium bicarbonate) that increase urine pH may decrease memantine clearance, resulting in elevated serum memantine concentrations and increased risk of adverse effects
- Trimethoprim may enhance the adverse/toxic effect of memantine. The risk of myoclonus and/or delirium may be increased. Trimethoprim may increase the serum concentration of memantine.

Memantine's Effect on Other Drugs

- Trimethoprim may enhance the adverse/toxic effect of memantine. The risk of myoclonus and/or delirium may be increased. Memantine may increase the serum concentration of trimethoprim.

Counseling Points

- Report any dizziness, headache, confusion, diarrhea, constipation, or hypertension
- Take as directed; follow the titration schedule until target dose of 10 mg twice daily is reached
- The oral solution should be administered using the dosing device with oral syringe provided by the manufacturer. Do not mix with any other liquid.

Key Points

- Avoid coadministration with drugs that can increase urine pH. Use caution under certain conditions that can increase urine pH (diet changes to vegetarian diet, renal tubular acidosis, severe urinary tract infections); these may decrease the clearance of memantine, resulting in increased concentrations and increased risk of adverse effects.
- Avoid coadministration with trimethoprim
- The tablet and oral solution formulations are interchangeable

SEDATIVE-HYPNOTIC AGENT, NONBENZODIAZEPINES

Introduction

A newer drug class of sedative-hypnotic medications has supplanted much of the use of benzodiazepines for treatment of insomnia. Although the nonbenzodiazepines do not resemble the benzodiazepines structurally, they do function in a similar fashion and have very similar side-effect profiles and patient Counseling Points. As with all sleep agents, caution needs to be exercised to prevent habitual use and disturbance of a patient's natural sleep pattern. With the exception of ramelteon, a hypnotic with a unique mechanism of action, these agents are Schedule IV medications and may be habit forming. Use should be limited in duration to prevent potential abuse, addiction, and increased reliance on higher dosing at bedtime.

Mechanism of Action for the Drug Class

Although not benzodiazepines, they also facilitate the activity of the inhibitory neurotransmitter GABA. Suvorexant's mechanism is slightly different in that it blocks orexin receptors and, in turn, suppresses the wake cycle. Ramelteon is a potent agonist of melatonin receptors, which play a role in circadian rhythms and the sleep–wake cycle.

Counseling Points for the Drug Class

- Sleep hygiene is the preferred first-line treatment for insomnia and should always be combined with pharmacologic therapy
- The failure of insomnia to remit after 7 to 10 days of therapy may indicate the presence of a primary psychiatric and/or other medical condition that should be evaluated
- Alcohol use while taking these medications can be dangerous and should be avoided
- Do not abruptly discontinue these drugs. A gradual taper is required to avoid rebound, relapse, and withdrawal symptoms. Insomnia is common after abruptly stopping sleeping aids.
- Only use when needed and for the shortest duration possible
- Take just before going to sleep and monitor for daytime alertness

Members of the Drug Class

In this section: zolpidem, eszopiclone, suvorexant
Others: ramelteon, zaleplon

◉ Zolpidem

Brand Names

Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist

Generic Name

Zolpidem

Rx Only

Class IV controlled substance

Dosage Forms

Tablet, sublingual tablet, spray

Usage

Short- and long-term treatment of insomnia

Pregnancy Category C

Dosing

- Initial dose:
  - Immediate-release tablet, sublingual, and spray: 5 mg (females), 5–10 mg (males) at bedtime
  - Extended-release tablet: 6.25 mg (females), 6.25–12.5 mg (males) at bedtime (1 spray = 5 mg)
- Hepatic dosage adjustment: Use with caution in patients with hepatic impairment:
  - Immediate-release tablet and spray: 5 mg at bedtime
  - Extended-release tablet: 6.25 mg at bedtime

Adverse Reactions: Most Common

Sedation, somnolence, dizziness, emergence of complex behavior ("sleep driving"), headache, diarrhea

Adverse Reactions: Rare/Severe/Important

Withdrawal syndromes and respiratory depression (especially with other CNS depressants or alcohol; use with caution in patients with mild to moderate COPD or sleep apnea), CNS depression, depression, anaphylaxis reactions (angioedema)

Major Drug Interactions

Major substrate of CYP3A4

Drugs Affecting Zolpidem

- Azole antifungal agents, ritonavir, and SSRIs: Increase serum concentrations
- Rifampin: Decreases serum concentrations

Zolpidem's Effect on Other Drugs

- CNS depressants: Additive CNS depression

Counseling Points

- Do not crush controlled-release tablets
- Place sublingual tablets under the tongue and do not swallow or administer with water

Key Points

- Use at the lowest effective dose for the shortest duration possible to minimize the potential for dependence and abuse that can occur with long-term use
- Reevaluate patient needs after 7 to 10 days of use. Zolpidem has been studied for use up to 35 days.
- Elderly patients are the most susceptible to side effects. Starting doses of the immediate-release, sublingual, and spray should be 5 mg at bedtime. The starting dose for the extended-release tablet should be 6.25 mg at bedtime.

- Use the immediate-release tablets for patients who require medication to initiate sleep. Use the extended-release tablets for patients who require medication to maintain sleep throughout the night.

Eszopiclone

Brand Name
Lunesta

Generic Name
Eszopiclone

Rx Only
Class IV controlled substance

Dosage Form
Tablet

Usage
Insomnia

Pregnancy Category C

Dosing
- Initial dose: 2 mg at bedtime
- Hepatic dosage adjustment: Use with caution in patients with mild-to-moderate hepatic impairment. For severe hepatic impairment, initial dose should be 1 mg (maximum 2 mg).

Adverse Reactions: Most Common
Headache, sedation, somnolence, dizziness, abnormal dreams, memory impairment, emergence of complex behavior ("sleep driving"), decreased inhibition, dry mouth, impaired coordination, unpleasant taste

Adverse Reactions: Rare/Severe/Important
Withdrawal syndromes and respiratory depression (especially with other CNS depressants or alcohol; use with caution in patients with compromised lung function), CNS depression, depression, anaphylaxis reactions (angioedema, throat closing, dyspnea), chest pain, peripheral edema

Major Drug Interactions
Major substrate of CYP3A4

Drugs Affecting Eszopiclone

Potent 3A4 inhibitors such as azole antifungal agents, clarithromycin, and ritonavir: Increase serum concentrations

Eszopiclone's Effect on Other Drugs

CNS depressants: Additive CNS depression

Key Points
- Use at the lowest effective dose for the shortest duration possible to minimize the potential for dependence and abuse that can occur with long-term use
- Reevaluate patient needs after 7 to 10 days of use. Eszopiclone has been studied for use up to 6 months.
- Elderly patients are the most susceptible to side effects. The starting dose should be 1 mg at bedtime.

Suvorexant

Brand Name
Belsomra

Generic Name
Suvorexant

Rx Only
Class IV controlled substance

Dosage Form
Tablet

Usage
Insomnia

Pregnancy Category C

Dosing
- Initial dose: 10 mg within 30 minutes of bedtime. Maximum dose: 20 mg.
- Use with moderate CYP3A4 inhibitors: Maximum dose 10 mg
- Use with strong CYP3A4 inhibitors: Use not recommended
- Hepatic dosage adjustment: Mild-to-moderate hepatic impairment, no dose adjustment is needed. For severe hepatic impairment, use is not recommended.

Adverse Reactions: Most Common
Sedation, dizziness, headache, abnormal dreams, memory impairment, CNS depression, hallucinations, sleep driving

Adverse Reactions: Rare/Severe/Important
Drug abuse, drug dependence, suicidal ideation

Major Drug Interactions
Major substrate of CYP3A4, minor substrate of CYP2C19

Drugs Affecting Suvorexant

Potent 3A4 inhibitors such as azole antifungal agents, clarithromycin, and ritonavir: Increase serum concentrations

Suvorexant's Effect on Other Drugs

CNS depressants: Additive CNS depression

Key Points
- Use at the lowest effective dose for the shortest duration possible to minimize the potential for dependence and abuse that can occur with long-term use
- Only take if you are planning to get a full night's sleep (at least 7 hours)

SKELETAL MUSCLE RELAXANTS, SPASMOLYTIC AGENTS

Introduction

Spasmolytic agents, which work in the CNS, reduce abnormally elevated tone and provide relief from skeletal muscle pain and discomfort. Many of them have a risk of dependence and are classified as controlled substances.

Mechanism of Action for the Drug Class

The exact mechanism of action is unclear, but the clinical effects of this class may be due to general depression of the CNS. These agents typically have no direct effect on skeletal muscle. Baclofen exerts its effects as an agonist at presynaptic $GABA_B$ receptors, acting mainly at the spinal cord level to inhibit the transmission of both monosynaptic and polysynaptic reflexes, with resultant relief of muscle spasticity. Cyclobenzaprine is structurally related to the tricyclic antidepressants (TCAs). It acts primarily at the brainstem within the CNS. Carisoprodol is metabolized to meprobamate, which has anxiolytic and sedative effects. Tizanidine is an imidazole derivative chemically related to clonidine, exhibiting alpha-2 adrenergic agonist properties.

Members of the Drug Class

In this section: Baclofen, carisoprodol, cyclobenzaprine, metaxalone, methocarbamol, tizanidine
Others: Chlorzoxazone, dantrolene, orphenadrine

◉ Baclofen

Brand Names

Gablofen, Lioresal

Generic Name

Baclofen

Rx Only

Dosage Forms

Injection, tablet

Usage

Treatment of muscle spasm associated with acute, painful musculoskeletal conditions; treatment of reversible spasticity associated with multiple sclerosis or spinal cord lesions; intractable hiccups, intractable pain relief, bladder spasticity, trigeminal neuralgia, cerebral palsy, alcohol abstinence, gastroesophageal reflux disease, Huntington's chorea

Pregnancy Category C

Dosing

- Oral: 5 mg 3 times a day, may increase 5 mg/dose every 3 days to a maximum of 80 mg daily
- Intrathecal:
  - Test dose: 50–100 µg, doses > 50 µg should be given in 25 µg increments, separated by 24 hours, until a 4- to 8-hour positive clinical response is seen. Patients not responding to the screening dose of 100 µg should not be considered for chronic infusion/implanted pump.
  - Maintenance: After positive response to test dose, a maintenance intrathecal infusion can be administered via an implanted intrathecal pump. Initial pump dose: Infusion at a 24-hourly rate dosed at twice the test dose.
- Renal dosage adjustment: May be necessary to reduce dosage; no specific guidelines have been established
- Geriatric dosing:
  - Use the lowest effective dose
  - Oral, initial: 5 mg two to 3 times daily, increasing gradually as needed; if no benefits are seen, withdraw drug slowly

Adverse Reactions: Most Common

Nausea, vomiting, drowsiness, dizziness, headache, poor muscle tone, weakness, hypotension

Adverse Reactions: Rare/Severe/Important

Constipation (significant with intrathecal use), withdrawal reactions with abrupt discontinuation (more severe with intrathecal use), coma, seizure

Major Drug Interactions

Avoid concomitant use with azelastine, methadone, par-aldehyde

Drugs Affecting Baclofen

- Droperidol, hydroxyzine increases the effect of baclofen

Baclofen's Effect on Other Drugs

- Baclofen increases the effect of alcohol, azelastine, buprenorphine, CNS depressants, SSRIs, and zolpidem
- Herbal considerations: Avoid valerian, St. John's wort, kava kava, gotu kola

Contraindications

Injectable product is for intrathecal use only; IV, epidural, SUB-Q, or IM administration is not recommended

Counseling Points

- Take as prescribed. Do not discontinue this medicine without consulting prescriber.
- Do not take any prescription or OTC sleep-inducing drugs, sedatives, or antispasmodics without consulting prescriber. Avoid alcohol use.
- Use caution when driving or engaging in tasks requiring alertness until response to drug is known
- Frequent small meals or lozenges may reduce GI upset

Key Points

- Avoid abrupt withdrawal of drug. Encourage consistent and early refills of medication to minimize the risk of significant sequelae of withdrawal.
- Avoid alcohol and other CNS depressants

Carisoprodol

Brand Name

Soma

Generic Name

Carisoprodol

Rx Only

Class IV controlled substance

Dosage Form

Tablet

Usage

Short-term treatment of muscle spasm associated with acute painful musculoskeletal conditions, pain associated with TMJ disorder

Pregnancy Category C

Dosing

- 250–350 mg 3 times daily and at bedtime
- Renal dosage adjustment: Use with caution in cases of renal impairment; not studied in this population
- Hepatic dosage adjustment: Use lower initial doses in cases of hepatic impairment and increase gradually as needed and tolerated

Adverse Reactions: Most Common

Dizziness, headache, somnolence

Adverse Reactions: Rare/Severe/Important

Paradoxical CNS stimulation, seizure, drug abuse/dependence, withdrawal symptoms

Major Drug Interactions

Avoid Concomitant Use

Azelastine, methadone, paraldehyde

Drugs Affecting Carisoprodol

- CYP2C19 inhibitors (moderate and strong), droperidol, hydroxyzine increase effect of carisoprodol
- CYP2C19 inducers (strong) decrease effect of carisoprodol

Carisoprodol's Effect on Other Drugs

- Concomitant use of carisoprodol with ethanol, CNS depressants, buprenorphine, methadone, SSRIs, zolpidem causes Additive CNS depression

Contraindications

Not recommended for use in geriatric patients or history of acute intermittent porphyria. Hypersensitivity reaction to a carbamate, such as meprobamate.

Counseling Points

- Do not use alcohol, prescription/OTC sedatives, CNS depressants, or psychotropic agents without consulting prescriber
- Use caution when driving, climbing stairs, or engaging in tasks requiring alertness
- Use caution when rising from sitting or lying position
- Report syncope, tachyarrhythmia, or excessive somnolence
- Report signs/symptoms of seizures when withdrawing from prolonged therapy
- Avoid meprobamate while on carisoprodol therapy
- Do not discontinue abruptly; taper dosage slowly to reduce risk of withdrawal symptoms

Key Points

- Carisoprodol should only be used for short periods (2 to 3 weeks) due to lack of evidence of effectiveness with prolonged use
- Carisoprodol is metabolized to meprobamate, which has anxiolytic and sedative effects. Avoid concurrent use of these two agents.

Cyclobenzaprine

Brand Names

Amrix, Fexmid, Flexeril

Generic Name

Cyclobenzaprine

Rx Only

Dosage Forms

Extended-release capsule, tablet

Usage

Treatment of muscle spasm associated with acute, painful musculoskeletal conditions, treatment of muscle spasm associated with acute TMJ

Pregnancy Category B

Dosing

- Extended-release capsule: 15 mg once daily; some patients may require up to 30 mg once daily
- Immediate-release tablet: 5 mg 3 times a day; may increase to 10 mg 3 times a day if needed
- Hepatic dosage adjustment:
  - Extended-release capsule: Not recommended in mild-to-severe impairment
  - Immediate-release tablet:
    - Mild impairment: Initial dose of 5 mg; use with caution; titrate slowly, and consider less frequent dosing
    - Moderate-to-severe impairment: Use not recommended
- Geriatric dosing:
  - Extended-release capsule: Use not recommended

- Immediate-release tablet: Initiate with a 5 mg dose and increase gradually as needed

Adverse Reactions: Most Common

Palpitations, nervousness, confusion, dizziness, headache, somnolence, bad taste in mouth, constipation, indigestion, nausea, dry mouth, blurred vision

Adverse Reactions: Rare/Severe/Important

Cholestasis, hepatitis, jaundice, cardiac dysrhythmia, anaphylaxis, immune hypersensitivity reaction

Major Drug Interactions

- Consider all drug interactions with TCAs as possible interactions with cyclobenzaprine due to their similar chemical structures
- *Avoid Concomitant Use*
- Azelastine, methadone, paraldehyde

Drugs Affecting Cyclobenzaprine

- Antipsychotics, CYP1A2 inhibitors: Increase level/effect

Cyclobenzaprine's Effect on Other Drugs

- Ethanol, CNS depressants, MAOIs: Increase level/effect
- Herbal considerations: Avoid valerian, kava kava, gotu kola (increased risk of CNS depression)

Contraindications

Arrhythmias, cardiac conduction disturbances, heart failure, heart block, acute recovery period following myocardial infarction, hyperthyroidism. Concomitant use with MAOI or use of MAOI within the past 14 days may cause hyperpyretic crisis, seizure, and death.

Counseling Points

- Avoid activities requiring mental alertness or coordination until drug effects are realized
- Watch for potential anticholinergic side effects
- Report signs/symptoms of decreased hepatic function, especially with preexisting hepatic disease
- Report lack of symptom improvement within 2 to 3 weeks of therapy
- Avoid alcohol and other CNS depressants while taking this drug
- Avoid concomitant use of TCAs during therapy with this drug

Key Points

- Not intended for long-term use. Do not use for > 2 to 3 weeks.
- Use caution in geriatric patients and in those with hepatic impairment
- Not effective for spasticity associated with cerebral palsy
- Given structural similarity to TCAs, advise patients of anticholinergic side effects and precautions. Avoid concomitant use with MAOIs.

Metaxalone

Brand Name

Skelaxin, Metaxall

Generic Name

Metaxalone

Rx Only

Dosage Form

Tablet

Usage

Treatment of muscle spasm associated with acute painful musculoskeletal conditions

Pregnancy Category Not Established/Use Not Recommended

Dosing

- Adults and children > 12 years: 800 mg 3 to 4 times a day
- Renal dosage adjustment: Use caution in mild-to-moderate impairment; no specific dosage recommendations; contraindicated with significant renal impairment
- Hepatic dosage adjustment: Use caution in mild-to-moderate impairment; no specific dosage recommendations; contraindicated with significant hepatic impairment

Adverse Reactions: Most Common

Drug-induced GI disturbances, nausea, vomiting, dizziness, headache, somnolence, nervousness

Adverse Reactions: Rare/Severe/Important

Hemolytic anemia, leukopenia, jaundice, hypersensitivity

Major Drug Interactions

- *Avoid Concomitant Use*
- Azelastine, methadone, paraldehyde

Metaxalone's Effect on Other Drugs

- Ethanol, CNS depressants, psychotropics, SSRIs: Increase level/effect
- Herbal considerations: Avoid valerian, St. John's wort, kava kava, gotu kola
- Food: Bioavailability may be increased; unclear clinical relevance

Test Interactions

- False positive for urine glucose determinations utilizing cupric sulfate, but the drug does not interfere with glucose tests using glucose oxidase (Benedict's solution)

Contraindications

History of drug-induced, hemolytic, or other anemias. Severe impairment in hepatic or renal function.

Essential Monitoring Parameters

Serum creatinine, liver function test, CBC

Counseling Points

- Avoid activities requiring mental alertness or coordination until drug effects are realized
- Inform diabetic patients that metaxalone may cause false-positive results for certain urine glucose tests
- Avoid alcohol and other CNS depressants while taking this drug
- If the next dose is > 1 hour past regular dosing time, skip the missed dose
- Report signs/symptoms of decreased hepatic function, especially with preexisting hepatic disease

Key Points

- Use caution in patients with significant renal or hepatic impairment
- May cause leukopenia; use caution with clozapine and carbamazepine
- Monitor relevant laboratory values for renal and hepatic function
- Serotonin syndrome can occur when used concomitantly with serotonergic drugs (e.g., tramadol, SSRIs) or when exceeding recommended doses

◉ Methocarbamol

Brand Names

Robaxin, Robaxin-750

Generic Name

Methocarbamol

Rx Only

Dosage Forms

Injection, tablet

Usage

Adjunctive treatment of muscle spasm associated with acute painful musculoskeletal conditions, supportive therapy in tetanus

Pregnancy Category C

Dosing

- Muscle spasm:
  - Oral: 1.5 g 4 times a day for 2 to 3 days (up to 8 g daily for severe conditions), then decrease to 4–4.5 g daily in 3 to 6 divided doses
  - IM, IV:
    - 1 g every 8 hours, if oral not possible
    - Maximum dose: 3 g daily for no more than 3 consecutive days
    - If condition persists, may repeat course of therapy after a drug-free interval of 48 hours
- Tetanus:
  - IV initial dose: 1–2 g by direct IV injection
  - Additional doses via infusion to maximum of 3 g total
  - May repeat dose every 6 hours until oral dosing is possible; injection should not be used for more than 3 consecutive days.
- Renal dosage adjustment: Use lower initial oral doses in cases of renal impairment and increase gradually as needed and tolerated
- Hepatic dosage adjustment:
  - Specific dosing guidelines are not available, plasma protein binding and clearance are decreased, half-life is increased
  - Use lower initial oral doses and increase gradually as needed and tolerated

Adverse Reactions: Most Common

Flushing, pruritus, rash, urticaria, indigestion, nausea, vomiting, dizziness, headache, nystagmus, somnolence, vertigo, nervousness, blurred vision, conjunctivitis

Adverse Reactions: Rare/Severe/Important

Bradyarrhythmia, hypotension, syncope, leukopenia, anaphylaxis, seizure (IV formulation)

Major Drug Interactions

- *Avoid Concomitant Use*
- Azelastine, methadone, paraldehyde

Drugs Affecting Methocarbamol

- Droperidol, CNS depressants: Increase level/effect

Methocarbamol's Effect on Other Drugs

- Ethanol, CNS depressants, SSRIs: Increases levels/effects
- Pyridostigmine: Decreases level/effect
- Herbal considerations: Avoid valerian, St. John's wort, kava kava, gotu kola

Contraindications

Injectable methocarbamol contains polyethylene glycol and is contraindicated in patients with renal dysfunction

Counseling Points

- Do not increase dose or discontinue without consulting prescriber. Take as directed.
- Avoid alcohol and other CNS depressants while taking this drug
- Avoid activities requiring mental alertness or coordination until drug effects are realized
- Drug may color urine brown, black, or green
- Report excessive drowsiness or mental agitation, chest pain, skin rash, swelling of mouth/face, difficulty speaking, or vision changes
- If the next oral dose is > 1 hour late, skip the missed dose

Key Points

- Do not use the injection formulation for more than 3 consecutive days

- Use caution in patients with renal and hepatic impairment
- Use injectable product with caution in patients with history of seizure
- Injectable product is *not* recommended in patients with renal dysfunction

◉ Tizanidine

Brand Name
Zanaflex

Generic Name
Tizanidine

Rx Only

Dosage Forms
Capsule, tablet

Usage
Management of spasticity, tension headaches, *low-back pain*, trigeminal neuralgia

Pregnancy Category C

Dosing
- Initial dose: 4 mg, may increase by 2–4 mg as needed for satisfactory reduction of muscle tone every 6 to 8 hours to a maximum of 3 doses totaling 36 mg in any 24-hour period
- Renal dosage adjustment: Reduce dose with a CrCl < 25 ml/min; clearance reduced > 50%
- Hepatic dosage adjustment: Avoid use if possible. If drug is necessary, use lowest possible doses while monitoring for hypotension. Extensive first-pass hepatic metabolism.
- Geriatric dosing: Clearance is decreased; dose cautiously. No specific dosing guidelines exist.

Adverse Reactions: Most Common
Hypotension, dry mouth, vomiting, constipation, abnormal liver function tests, dizziness, somnolence, nervousness, muscle weakness, speech, or vision disturbances

Adverse Reactions: Rare/Severe/Important
Orthostatic hypotension, angina, heart failure, myocardial infarction, syncope, leukopenia, thrombocytopenia, hepatitis

Major Drug Interactions
- *Avoid Concomitant Use*
- Azelastine, ciprofloxacin, fluvoxamine, paraldehyde

Drugs Affecting Tizanidine
- Beta blockers, ciprofloxacin, CYP1A2 inhibitors, fluvoxamine, herbal products with hypotensive properties, hydroxyzine, MAOIs, estrogens, phosphodiesterase 5 inhibitors, pentoxifylline: Increase effects
- Antidepressants (alpha-2 antagonists), herbal products with hypertensive properties, methylphenidate, SSRIs/SNRIs, TCAs: Decrease effects

Tizanidine's Effect on Other Drugs
- Ethanol, CNS depressants, antihypertensives (ACE inhibitors), QTc-prolonging agents, SSRIs: Increase effects
- Herbal considerations: Avoid valerian, St. John's wort, kava kava, gotu kola (increase CNS depression); avoid black cohosh, hawthorn, mistletoe, periwinkle, poppy, quinine (increase hypotensive effects)

Contraindications
Concomitant therapy with ciprofloxacin or fluvoxamine (potent CYP1A2 inhibitors)

Essential Monitoring Parameters
Hepatic function (aminotransferase): Measure at baseline, then at 1, 3, and 6 months of therapy, and periodically thereafter, based on clinical status

Counseling Points
- Avoid activities requiring mental alertness until drug effects are realized
- Rise slowly from a lying/seated position because this drug may cause hypotension
- Although this drug may be taken with or without food, take the drug the same way every time. Inconsistent administration with regard to food may enhance or delay onset and change the adverse-effect profile.
- Do not discontinue the drug suddenly
- Do not drink alcohol while taking this drug

Key Points
- Tizanidine is chemically related to clonidine and has alpha-2 adrenergic agonist properties
- Use with caution in the elderly
- Discuss risks of sudden discontinuation of drug
- Follow maximum daily dosing guidelines

SKELETAL MUSCLE RELAXANTS, ACETYLCHOLINESTERASE INHIBITORS

Introduction

Acetylcholinesterase inhibitors work at the skeletal neuromuscular junction to promote impulse transmission and muscle contraction in muscles weakened by neuromuscular blocking agents or myasthenia gravis. Some have been used in eye drops to treat glaucoma.

Mechanism of Action for the Drug Class

Pyridostigmine inhibits destruction of acetylcholine by acetylcholinesterase, which promotes transmission of impulses across the neuromuscular junction. This increases the strength of contraction, especially in muscles weakened by neuromuscular blocking agents or by myasthenia gravis.

Members of the Drug Class

In this section: pyridostigmine
Others: edrophonium, neostigmine

◉ Pyridostigmine

Brand Names

Mestinon; Mestinon Timespan; Regonol

Generic Name

Pyridostigmine

Rx Only

Dosage Forms

Tablet, Extended release tablet, syrup, injection

Usage

Myasthenia gravis; reversal of nondepolarizing muscle relaxants, pretreatment for Soman nerve gas exposure (military use)

Pregnancy Category B/C (manufacturer dependent)

Dosing

- Myasthenia Gravis:
  - Immediate release: Initial dose 60–1500 mg/day, usually 600 mg/day divided into 5 to 6 doses, spaced to provide maximum relief
  - Extended release: Initial dose 180–540 mg once or twice daily. It may be necessary to use immediate release in conjunction.
  - IM or slow IV injection: give 1/30th of the oral dose. For myasthenic crisis, continuous infusion 1–2 mg/hour with gradual titration in increments of 0.5–1 mg to max of 4 mg/hour may be used.
  - Reversal of nondepolarizing muscle relaxants: IV 0.1–0.25 mg/kg/dose

Adverse Reactions: Most Common

- Abdominal cramping and diarrhea; salivation; sweating; urinary incontinence
- Rash due to bromide salt of pyridostigmine

Adverse Reactions: Rare/Severe/Important

- Cholinergic crisis due to overdosage of pyridostigmine may occur (e.g., muscle weakness, bradycardia, respiratory failure), which must be distinguished from drug-resistant myasthenia crisis. Discontinue immediately in presence of cholinergic crisis. Timing of onset of muscle weakness can help distinguish between overdosage or underdosage of pyridostigmine. Symptoms that occur within 1 hour of drug administration may suggest cholinergic crisis and symptoms that occur after 3 hours of pyridostigmine administration are likely due to drug-resistant myasthenia crisis.
- Cardiac arrest can occur with IV administration; IM route is the preferred parenteral route for myasthenia gravis

Major Drug Interactions

Drugs Affecting Pyridostigmine

- Anticholinergic agents may diminish therapeutic effect of pyridostigmine

Pyridostigmine's Effect on Other Drugs

- Succinylcholine: Increase drug levels
- Beta-blockers: Increase bradycardia

Contraindications

Mechanical intestinal or urinary obstruction
Cross-reactivity for allergy to other anticholinergic agents is possible

Essential Monitoring Parameters

Vital capacity

Counseling Points

- Report symptoms of worsening muscle weakness, diarrhea, or cramping
- Report rash

Key Points

- LOOK ALIKE/SOUND ALIKE alert: Do not confuse with physostigmine
- Pyridostigmine blocks the destruction of acetylcholine by acetylcholinesterase, allowing neurotransmission of impulses across the neuromuscular junction
- Primarily used to improve muscle weakness in patients with myasthenia gravis; pyridostigmine dosing is highly individualized based on achievement of

goal-vital capacity and avoidance of significant diarrhea. Overdosages (e.g., cholinergic crisis) may occur during dose escalation for myasthenia crisis. Atropine should be readily available during treatment of myasthenia crisis.

- In case of cholinergic crisis (e.g., bradycardia, worsening muscle weakness), discontinue pyridostigmine immediately and give atropine. Muscle weakness from cholinergic crisis must be distinguished from myasthenic crisis. Note onset of symptoms relative to dose. If symptoms occur within 1 hour of dose, cholinergic crisis is likely. If symptoms occur after 3 hours of parenteral dose, myasthenic crisis is likely.

STIMULANTS

Introduction

The CNS stimulants are primarily used in the treatment of ADHD, narcolepsy, and excessive daytime sleepiness (EDS). Stimulants increase alertness and prevent sleep, but their side-effect profile includes insomnia, heart palpitations, hypertension, irritability, and, in more severe cases, serious cardiac events, including sudden death. In addition to their side-effect profile, another downside to stimulants is that they are controlled substances with the potential for abuse and addiction. The goal of using these agents is to improve quality of life while finding a balance between benefit and risk.

Mechanism of Action for the Drug Class

Although the mechanism of action for modafinil is unknown, the other drugs covered in this class are thought to mediate CNS stimulation through either the release of norepinephrine and dopamine (e.g. amphetamine/dextroamphetamine) or through blocking the reuptake of norepinephrine and dopamine (e.g. methylphenidate)

Counseling Points for the Drug Class

- Avoid alcohol and caffeine
- Avoid evening doses to prevent insomnia
- Consult physician before discontinuing the medication
- Counsel patients about the potential adverse effects on sleep, mood, and appetite. Counsel on the black box warning for both addiction and serious cardiac events. Tell patient to report chest pain, difficulty breathing, fainting, abnormal thinking or behavior, increased aggression, hallucinations, and weight loss.

Key Points for the Drug Class

- **Black Box Warning:**
  - With the exception of modafinil, all stimulant medications have warnings, one for abuse/addiction potential and one for serious cardiac events, including sudden death. It is, therefore, prudent to screen and monitor cardiovascular risk, blood pressure, heart rate, psychiatric status, growth parameters, weight gain, appetite, and signs of tolerance, abuse, or addiction. These same monitoring parameters should also be employed for modafinil.
- When using stimulants for the treatment of ADHD, consider obtaining an ECG prior to therapy. The clinical role of routine ECG monitoring has yet to be determined.
- When using stimulants for non-ADHD indications, monitor for daytime alertness
- Drug holidays may be given to children to determine the need for continued treatment and to allow for "catch-up" growth

Members of the Drug Class

In this section: Amphetamine/dextroamphetamine, methylphenidate, lisdexamfetamine, modafinil
Others: Armodafinil, dextroamphetamine, methamphetamine, dexmethylphenidate

◉ Amphetamine/Dextroamphetamine

Brand Names

Adderall, Adderall XR

Generic Name

Amphetamine/dextroamphetamine

Rx Only

Class II controlled substance

Dosage Forms

Immediate-release tablet, extended-release capsule

Usage

ADHD, narcolepsy

Pregnancy Category C

Dosing

- ADHD:
  - Adults:
    - Immediate-release tablet:

- Initial dose: 5 mg 1 to 2 times a day
- Maximum dose: 40 mg daily

- Extended-release capsule:
  - Initial dose: 20 mg daily in the morning
  - Maximum dose: 60 mg daily (lack of adequate data that doses this high provide additional benefit)

- Children:
  - Initial dose:
    - 3 to 5 years of age:
      - Immediate-release tablet: 2.5 mg daily; maximum 40 mg daily
    - 6 years or older:
      - Immediate-release tablet: 5 mg daily one to 2 times a day; maximum 40 mg daily
      - Extended-release capsule: 5–10 mg daily; maximum 30 mg daily
  - Give the first dose on awakening
  - Multiple doses of immediate-release tablets should be dosed at intervals of 4 to 6 hours

- Narcolepsy:
  - Adults:
    - Initial dose: Immediate release 10 mg daily
    - Maximum dose: 60 mg daily
  - Children:
    - 6 to 12 years of age: Initial dose 5 mg daily
    - > 12 years of age: Refer to adult dosing

Adverse Reactions: Most Common

Insomnia, headache, weight loss, loss of appetite, nervousness, abdominal pain, tachycardia

Adverse Reactions: Rare/Severe/Important

Cardiac adverse effects, including sudden death; drug abuse/dependency; sudden death in children; suppression of growth in children with long-term use; exacerbation of preexisting or emergence of new psychiatric disorders; worsening of motor and vocal tics; aggression; seizures; visual disturbances; dependency

Major Drug Interactions

Contraindicated with concomitant use of MAOIs or within 14 days of MAOI use

Drugs Affecting Amphetamine/Dextroamphetamine

- Antacids, acetazolamide, thiazides: Increase levels
- Urinary alkalinizing agents: Increase levels
- Urinary acidifying agents: Decrease levels
- Norepinephrine and other stimulants: Increase effects

Amphetamine/Dextroamphetamine's Effect on Other Drugs

- Other CNS stimulants: Additive effects

Contraindications

Advanced arteriosclerosis, symptomatic cardiovascular disease, cardiac structure abnormalities, hypertension, hyperthyroidism, glaucoma, agitated states, history of drug abuse, hypersensitivity, or idiosyncratic reactions to the sympathomimetic amines, during or within 14 days following MAO inhibitor

Essential Monitoring Parameters

CNS activity, blood pressure, heart rate, weight, growth parameters; appetite; signs/symptoms of tolerance or dependence, consider obtaining ECG prior to initiation

Counseling Point

Do not crush or chew sustained-release formulations. The contents of the capsules may be sprinkled on applesauce.

Key Points

- Amphetamine/dextroamphetamine has many contraindications (see above) due to the possibility of serious cardiac complications, including sudden cardiac death as well as the potential for abuse and addiction. There is a black box warning for both abuse potential and serious cardiovascular events with this agent.
- Screen and monitor cardiovascular risk, blood pressure, heart rate, psychiatric history, growth parameters, weight gain, and signs of abuse

Methylphenidate

Brand Names

Ritalin, Ritalin LA, Concerta, Methylin, Metadate ER, Metadate CD, Daytrana, QuilliChew ER, Quillivant XR

Generic Name

Methylphenidate

Rx Only

Class II controlled substance

Dosage Forms

Immediate-release, sustained-release, and extended-release tablets; extended-release capsule; chewable tablet; transdermal system; solution; suspension

Usage

ADHD, narcolepsy, depression, fatigue

Pregnancy Category C

Dosing

- ADHD:
  - Adults:
    - Immediate release:
      - Initial dose of 10–60 mg daily in 2 to 3 divided doses
      - Maximum dose: 60 mg daily
    - Extended release:
      - Initial dose: 20 mg daily in the morning
      - Maximum dose: 60 mg daily
  - Sustained- and extended-release tablets have an 8-hour duration of action. Administer the 8-hour dose of the regular-release tablets.
  - Concerta: Initial dose 18–36 mg once a day

- Metadate CD: Initial dose 20 mg once a day
- Daytrana 10 mg patch: Apply to clean, dry, intact skin on hip area 2 hours before effect is needed; remove 9 hours after application
- Children > 6 years of age: Immediate-release 5 mg twice a day

- Narcolepsy:
  - Initial dose: Immediate-release 5 mg twice a day
  - Maximum dose: 60 mg daily

Adverse Reactions: Most Common

Insomnia, headache, anorexia, loss of appetite, nervousness, dizziness, hyperhidrosis, nausea, tachycardia

Adverse Reactions: Rare/Severe/Important

Serious cardiac adverse events, abuse/addiction/dependency, sudden death in children, suppression of growth in children with long-term use, exacerbation of preexisting or emergence of new psychiatric disorders, worsening of motor and vocal tics, aggression, seizures, visual disturbances, contact dermatitis with transdermal application, thrombocytopenia

Major Drug Interactions

Concomitant use with MAOIs or halogenated anesthetics is contraindicated

Methylphenidate's Effect on Other Drugs

SSRIs and warfarin: Increases serum concentrations

Contraindications

- Structure cardiac abnormalities, advanced arteriosclerosis, symptomatic heart disease, moderate to severe hypertension, history of drug abuse, hypersensitivity or idiosyncratic reactions to sympathomimetic amines, glaucoma, anxiety and agitated states, motor tics, family history or diagnosis of Tourette's syndrome, use during or within 14 days following MAO inhibitor therapy
- Metadate CD and Metadate ER have additional contraindications of severe hypertension, heart failure, arrhythmias, hyperthyroidism, recent myocardial infarction or angina, and concomitant use of halogenated anesthetics

Essential Monitoring Parameters

CNS stimulation, blood pressure, heart rate, weight, growth parameters; appetite; signs/symptoms of tolerance or dependence, signs and symptoms of depression, aggression, hostility, suicidal behavior/ ideation, consider obtaining ECG prior to initiation

Counseling Points

- Do not crush or chew sustained- or extended-release formulations. The contents of the capsules may be sprinkled on applesauce.
- Take immediate-release tablets, chewable tablets, and solution 30 to 45 minutes before meals
- Drink at least 8 ounces of water with chewable tablets to avoid choking

Key Points

- Methylphenidate has many contraindications due to the potential for serious cardiac complications, including sudden cardiac death and the potential for abuse (see previous discussion). Use with caution in patients with hypertension and other cardiovascular conditions that might be exacerbated by increases in blood pressure or heart rate.
- Screen and monitor cardiovascular risk, psychiatric history, growth parameters, weight changes, and signs of abuse

◉ Lisdexamfetamine

Brand Name

Vyvanse

Generic Name

Lisdexamfetamine

Rx Only

Class II controlled substance

Dosage Form

Capsule

Usage

ADHD, binge eating disorder

Pregnancy Category

Lisdexamfetamine is converted to dextroamphetamine. The majority of human data is based on illicit amphetamine/methamphetamine exposure. Use of amphetamines during pregnancy may lead to an increased risk of premature birth and low birth weight; newborns may experience symptoms of withdrawal.

Dosing

- ADHD
  - Adults and children 6 years and older:
  - Initial dose: 30 mg once daily in the morning
  - Dosage adjustment: May increase by 10–20 mg daily at weekly intervals until optimal response
  - Maximum dose: 70 mg daily
  - Administer at lowest effective dose and individualize based on patient response
- Binge eating disorder
  - Initial dose: 30 mg once daily in the morning
  - Dosage adjustment: May increase by 20 mg daily at weekly intervals until optimal response
  - Maximum dose: 70 mg daily
  - Discontinue if binge eating does not improve

Adverse Reactions: Most Common

Headache, insomnia, irritability, decreased appetite and weight, xerostomia, abdominal pain, nausea, vomiting

Adverse Reactions: Rare/Severe/Important

Cardiac adverse effects, including sudden death; drug abuse/addiction/dependency; sudden death in children; suppression of growth in children with long-term use; exacerbation of preexisting or emergence of new psychiatric disorders; worsening of motor and vocal tics; aggression; seizures; visual disturbances

Major Drug Interactions

Drugs Affecting Lisdexamfetamine

- Urinary alkalinizing agents: Increase levels
- Urinary acidifying agents: Decrease levels
- Norepinephrine and other stimulants: Increase effects

Lisdexamfetamine's Effect on Other Drugs

- Adrenergic blockers, antihistamines, antihypertensives, phenobarbital, phenytoin: May reduce effects
- TCAs and meperidine: May potentiate effects

Contraindications

Concurrent use of MAO inhibitor, or within 14 days of the last MAO inhibitor dose

Counseling Points

- May be taken with or without food
- Capsules can be taken whole or they can be opened and the entire contents of the capsule can be dissolved in a glass of water. The solution must be drunk immediately and not stored.
- The dose of a single capsule should not be divided
- The patient should not take less than one capsule per day

Key Point

Screen and monitor cardiovascular risk, blood pressure, heart rate, psychiatric status, abuse potential, growth parameters, and weight changes

◉ Modafinil

Brand Name

Provigil

Generic Name

Modafinil

Rx Only

Class IV controlled substance

Dosage Form

Tablet

Usage

Narcolepsy, shift work sleep disorder, obstructive sleep apnea, ADHD, fatigue, major depressive disorder (antidepressant augmentation), multiple sclerosis-related fatigue

Pregnancy Category C

Dosing

- ADHD: Initial dose of 100–400 mg daily
- Narcolepsy and obstructive sleep apnea: Initial dose of 200 mg daily taken in the morning
- Shift-work sleep disorder: Initial dose of 200 mg daily taken 1 hour prior to shift work
- Doses of up to 400 mg daily have been well tolerated, but there is no evidence that this dose confers additional benefit
- Hepatic dosage adjustment: Reduce dose by 50% in patients with severe hepatic impairment

Adverse Reactions: Most Common

Insomnia, headache, nervousness, dizziness, nausea, anxiety, decreased appetite, and abdominal pain in children

Adverse Reactions: Rare/Severe/Important

Hypertension, rash, Stevens-Johnson syndrome, multiorgan hypersensitivity reaction, angioedema, anaphylaxis, psychiatric symptoms, aggressive behavior

Major Drug Interactions

- Major substrate of CYP3A4
- Weak inhibitor of CYP2C19, CYP2C9
- Weak/moderate inducer of CYP1A2, and 3A4

Drugs Affecting Modafinil

- CYP3A4 inhibitors: Increase concentrations
- CYP3A4 inducers: Decrease concentrations

Modafinil's Effect on Other Drugs

- Oral contraceptives: Decreases serum concentrations

Essential Monitoring Parameters

- Levels of sleepiness; blood pressure; heart rate; increased monitoring in patients with recent MI or unstable angina; development of severe skin reactions; development or exacerbation of psychiatric symptoms (e.g., agitation, anxiety, depression)
- When used for the treatment of ADHD, thoroughly evaluate for cardiovascular risk. Monitor heart rate, blood pressure, and consider obtaining ECG prior to initiation.

Counseling Point

If using oral contraceptives, consider an additional or alternative method of birth control

Key Points

- Modafinil is a schedule IV medication that can produce psychoactive and euphoric effects, which can lead to abuse and addiction. Because it is a C-IV and not a C-II, the abuse potential is slightly less compared with other CNS stimulants.
- Warnings are listed for severe dermatologic reactions, including serious and life-threatening rashes (including Stevens-Johnson syndrome) and to use with caution in patients with cardiovascular disease; therefore, monitor for development of skin reactions and monitor heart rate, blood pressure, and consider obtaining ECG prior to initiation.

NONSTIMULANT ADHD AGENT, ALPHA-2 ADRENERGIC AGONIST

Introduction

As a treatment for ADHD, guanfacine is a unique medication that works differently than traditional stimulants or modafinil. The extended-release tablets are primarily used for the management of ADHD, although the immediate-release tablets are indicated for the management of hypertension. It is used infrequently for hypertension, given the availability of safer and better tolerated agents. In contrast to most ADHD medications, guanfacine is a noncontrolled substance. It has not been shown to cause abuse or addiction, making it a good option for patients with a history of drug abuse. Guanfacine also differs from other ADHD medications in that it is not a CNS stimulant and can, in fact, cause marked CNS depression. It can be used alone or in combination with stimulants, but prolonged use for maintenance treatment greater than 9 weeks' duration has not been studied.

Mechanism of Action for the Drug Class

Guanfacine is a selective alpha-2A adrenoreceptor agonist, which reduces sympathetic nerve impulses, resulting in reduced sympathetic outflow and a subsequent decrease in vasomotor tone and heart rate. In addition, guanfacine preferentially binds postsynaptic alpha-2A adrenoreceptors in the prefrontal cortex and has been theorized to improve delay-related firing of prefrontal cortex neurons. As a result, underlying working memory and behavioral inhibition are affected, thereby improving symptoms associated with ADHD.

Members of the Drug Class

In this section: Guanfacine

◉ Guanfacine

Brand Names

Intuniv

Generic Name

Guanfacine

Rx Only

Dosage Forms

Immediate- and extended-release tablets

Usage

ADHD, as primary or adjunctive therapy to stimulants

Pregnancy Category B

Dosing

- Extended-release tablets for the treatment of ADHD in patients 6 years and older:
  - Initial dose: 1 mg once daily
  - Dosage adjustment: Dose may be adjusted by increments no larger than 1 mg/week as tolerated, based on clinical response. Note that in clinical trials, significant adverse events were dose- and exposure-related, thus consideration should be given to dosing on a mg/kg basis (initial: 0.05–0.08 mg/kg, if tolerated can increase to 0.12 mg/kg, with a max of 7 mg).
- If a patient misses 2 or more consecutive doses, repeat titration of dose should be considered
- Discontinuation: Taper the dose in decrements of no more than 1 mg every 3 to 7 days
- Do not substitute extended-release tablets for immediate-release tablets on a mg-per-mg basis because of differing pharmacokinetic profiles
- Renal dosage adjustment: No specific dose adjustments are recommended in renal dysfunction, although adjustments may be required based on clinical response
- Hepatic dosage adjustment: No specific dose adjustments are recommended in hepatic dysfunction, although adjustments may be required based on clinical response

Adverse Reactions: Most Common

Somnolence, sedation, dizziness, headache, fatigue, xerostomia, constipation, abdominal pain, hypotension, bradycardia, syncope

Adverse Reactions: Rare/Severe/Important

Severe hypotension, bradycardia, syncope, sedation, somnolence, atrioventricular block, sinus arrhythmia, abnormal liver function tests

Major Drug Interactions

Major substrate of CYP3A4

Drugs Affecting Guanfacine

- CYP3A4 inhibitors such as ketoconazole: Increase concentrations
- CYP3A4 inducers such as rifampin: Decrease concentrations

Guanfacine's Effect on Other Drugs

- Valproic acid: Increases concentrations
- Warning of concomitant use with MAOIs due to risk of hypertensive crisis
- Antihypertensives (hypotension) or CNS depressants (CNS depression): Additive effects

Essential Monitoring Parameters

CNS activity; When used for the treatment of ADHD, thoroughly evaluate for cardiovascular risk. Monitor heart rate, blood pressure (prior to initiation, following dosage adjustments, and periodically thereafter), and consider obtaining ECG prior to initiation

Counseling Points

- Avoid excessive alcohol
- Do not crush or chew extended-release tablets
- Take with a full glass of water and maintain adequate hydration unless otherwise restricted
- Do not take with a high-fat meal because of increased absorption
- Sedation can occur, especially after therapy initiation or dose escalation
- Report excessive drowsiness or dizziness, respiratory difficulty, or GI changes
- Do not stop abruptly without tapering

Key Points

- Guanfacine is a non-controlled medication used to treat ADHD. Abuse potential is much lower than with stimulant medications.
- Guanfacine can cause significant, dose-dependent CNS depression, hypotension, and bradycardia
- Doses should be escalated gradually and tapered for discontinuation. If a patient misses 2 or more doses, dose retitration should be employed.
- For ADHD, guanfacine can be used alone or in combination with stimulants, although its use as maintenance treatment for longer than 9 weeks has not been evaluated

REVIEW QUESTIONS

1. Which of the following seizure medications is commonly used to treat fibromyalgia?
   - a. Phenytoin
   - b. Pregabalin
   - c. Phenobarbital
   - d. Carbamazepine

2. Which of the following antiepileptic drugs can be used in status epilepticus?
   - a. Lamotrigine
   - b. Levetiracetam
   - c. Oxcarbazepine
   - d. Topiramate

3. The target serum concentration for carbamazepine is:
   - a. 4–12 µg/ml
   - b. 10–20 µg/ml
   - c. 10–40 µg/ml
   - d. 50–100 µg/ml

4. Which of the following AEDs is most associated with drug interactions?
   - a. Gabapentin
   - b. Valproic acid
   - c. Lamotrigine
   - d. Levetiracetam

5. Which of the following should be avoided in patients with a sulfonamide allergy?
   - a. Lamotrigine
   - b. Oxcarbazepine
   - c. Topiramate
   - d. Zonisamide

6. Which of the following muscle relaxants is most commonly used to reduce spasticity in patients with multiple sclerosis?
   - a. Cyclobenzaprine
   - b. Baclofen
   - c. Pyridostigmine
   - d. Skelaxin

7. Which of the following drugs has an active metabolite named MHD?

   a. Valproic Acid
   b. Phenobarbital
   c. Oxcarbazepine
   d. Gabapentin

8. Which of the following drugs does the FDA require a negative pregnancy test prior to initiation of therapy?

   a. Qsymia
   b. Valproic Acid
   c. Topiramate
   d. Zonisamide

9. Which of the following is NOT a contraindication for use of rizatriptan?

   a. History of MI
   b. History of stroke
   c. Use of MAOI within the past 14 days
   d. Uncontrolled diabetes

10. Which of the following agents is most likely to cause hyponatremia?

    a. Carbamazepine
    b. Topiramate
    c. Valproic acid
    d. Levetiracetam

11. Which of the following antidepressants can be used off-label for insomnia?

    a. Venlafaxine
    b. Citalopram
    c. Vortioxetine
    d. Trazodone

12. The maximum daily dose of citalopram for patients greater than 60 years old is:

    a. 40 mg
    b. 60 mg
    c. 10 mg
    d. 20 mg

13. Which of the listed agents is the atypical antipsychotic with the highest incidence of causing QTc-prolongation?

    a. Risperidone
    b. Haloperidol
    c. Ziprasidone
    d. Olanzapine

14. The risk for extrapyramidal effects with risperidone use is highest at doses above:

    a. 2 mg
    b. 3 mg
    c. 4 mg
    d. 6 mg

15. Which of the following atypical antipsychotics has the *highest* incidence of weight gain?

    a. Abilify
    b. Zyprexa
    c. Seroquel
    d. Geodon

16. Which of the following is a common side effect of cholinesterase inhibitors?

    a. Bradycardia
    b. Tachycardia
    c. Constipation
    d. Hypotension

17. Which of the following side effects are more common with typical antipsychotics compared with atypical antipsychotics?

    a. Extrapyramidal effects
    b. Weight gain
    c. Glucose intolerance
    d. Sexual dysfunction

18. Which of the following antipsychotics is available coformulated with an antidepressant?

    a. Olanzapine
    b. Risperidone
    c. Quetiapine
    d. Ziprasidone

19. The maximum dose of Ambien for women is:

    a. 2.5 mg
    b. 5 mg
    c. 10 mg
    d. 12.5 mg

20. Which of the following antidepressants is good for patients with associated loss of appetite or weight loss?

    a. Sertraline
    b. Fluoxetine
    c. Mirtazapine
    d. Duloxetine

21. Which of the following agents is a non-benzodiazepine antianxiety agent?

    a. Alprazolam
    b. Buspirone
    c. Clonazepam
    d. Lorazepam

22. Which of the following agents has a black box warning for serious cardiovascular events, including sudden death in patients with preexisting structural cardiac abnormalities or other serious heart problems?

    a. Buspirone
    b. Diazepam
    c. Dextroamphetamine and amphetamine
    d. Modafinil

23. Which of the following agents is contraindicated with concomitant use of MAOIs or within 14 days of MAOI use?

- **a.** Methylphenidate
- **b.** Ambien
- **c.** Citalopram
- **d.** Lorazepam

24. Which of the following agents used for narcolepsy has a lower abuse potential compared with other CNS stimulants, therefore, is a Class IV controlled substance instead of a Class II controlled substance?

- **a.** Modafinil
- **b.** Methylphenidate
- **c.** Amphetamine/dextroamphetamine
- **d.** Lisdexamfetamine

25. A drug interaction between lorazepam and CNS depressants/alcohol can potentially result in:

- **a.** Increase in CNS depression
- **b.** Decrease in CNS depression
- **c.** Increase in CNS stimulation
- **d.** Decrease in CNS stimulation

26. Which of the following benzodiazepines has a risk of propylene glycol toxicity occurring when using the parenteral formulation for a prolonged period of time?

- **a.** Temazepam
- **b.** Lorazepam
- **c.** Alprazolam
- **d.** Clonazepam

27. Which of the following agents has a black box warning for concomitant use with opioids as it may result in profound sedation, respiratory depression, coma, and death?

- **a.** Duloxetine
- **b.** Eletriptan
- **c.** Methylphenidate
- **d.** Temazepam

28. What is an indication for guanfacine?

- **a.** Seizures
- **b.** ADHD
- **c.** Neuropathic pain
- **d.** Major depressive disorder

29. Which selective alpha-2A adrenoreceptor agonist, has an adverse effect of potentially causing hypotension, especially when used in combination with an antihypertensive?

- **a.** Metaxalone
- **b.** Rivastigmine
- **c.** Guanfacine
- **d.** Levetiracetam

30. Which of the following agents has a black box warning concerning a maximum IV infusion rate of 50 mg/min due to a risk of hypotension and cardiac arrhythmias?

- **a.** Levetiracetam
- **b.** Fosphenytoin
- **c.** Phenytoin
- **d.** Lorazepam

CHAPTER 7

Endocrine Agents

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BISPHOSPHONATES

Introduction

Bisphosphonates are used in the treatment and prevention of osteoporosis. The specific dosing instructions provided can prevent the common GI side effects mainly seen with the oral formulations. Many of them have multiple dosing options, often for the same indications, such as osteoporosis.

Mechanism of Action for the Drug Class

Bisphosphonates have two phosphonate groups that mimic the action of pyrophosphate, an endogenous inhibitor of bone resorption. This leads to decreased osteoclast activity and the prevention of bone destruction. All bisphosphonates become incorporated into the bone, giving them extensive half-lives.

Usage for the Drug Class

Osteoporosis, Paget's disease, hypercalcemia, bone metastasis from solid tumors

Adverse Reactions for the Drug Class: Most Common

Abdominal pain, dyspepsia, nausea, hypocalcemia

Adverse Reactions for the Drug Class: Rare/Severe/Important

Bone/muscle pain, esophagitis, gastritis, esophageal ulcers, osteonecrosis of the jaw

Major Drug Interactions for the Drug Class

Drugs Affecting Bisphosphonates

- Aspirin: Increases risk of adverse GI events
- Nonsteroidal anti-inflammatory drugs (NSAIDs): Increase risk of GI irritation
- Antacids: Decrease absorption of oral bisphosphonates

Contraindications for the Drug Class

Patients with abnormalities of the esophagus, such as strictures or achalasia. Inability to sit upright or stand for at least 30 minutes.

Counseling Points for Oral Bisphosphonates

- Take at least 30 minutes before eating or drinking first thing in the morning. Take with 6 to 8 oz. of plain water only.
- Do not lie down for 30 minutes after taking the medication and until after the first meal of the day
- Do not chew or crush tablets. Effervescent tablets will dissolve in water.
- Notify your physician if new symptoms of heartburn or difficulty or pain on swallowing develop
- Take supplemental calcium and vitamin D if dietary intake is inadequate

Key Points for the Drug Class

- Bisphosphonates are first line for the treatment of osteoporosis
- Special administration techniques for oral bisphosphonates are needed in order to prevent GI problems
- Hypocalcemia must be corrected before therapy is initiated
- Osteonecrosis of the jaw, usually related to tooth extraction and/or local infection with delayed healing, has been observed with the use of bisphosphonates. Bisphosphonate-associated osteonecrosis has been reported primarily in cancer patients receiving intravenous bisphosphonates. However, some cases have also been reported in patients receiving treatment for postmenopausal osteoporosis. The known risk factors for osteonecrosis include a cancer diagnosis, poor oral hygiene, concomitant therapies (i.e., radiotherapy, chemotherapy, corticosteroids), and comorbid diseases (i.e., preexisting dental disease, anemia, infection, coagulopathy). Patients who develop osteonecrosis of the jaw should be referred to an oral surgeon for care.
- Patients with GERD or other GI problems may be better candidates for intravenous administration of bisphosphonates (such as zoledronic acid)

- Atypical femur fractures have been reported in patients receiving bisphosphonates for treatment/prevention of osteoporosis
- Consider discontinuing after 3 to 5 years of use for osteoporosis in patients at low-risk for fracture.

Members of the Drug Class

In this section: Alendronate, risedronate, ibandronate, zoledronic acid
Others: Etidronate, pamidronate, clodronate, tiludronate

Alendronate

Brand Names
Fosamax, Fosamax Plus D, Binosto

Generic Name
Alendronate

Rx Only

Dosage Forms
Tablet, effervescent tablet, solution

Pregnancy Category C

Dosing
- Treatment of osteoporosis in men and postmenopausal women: 70 mg once a week *or* 10 mg daily
- Prevention of postmenopausal osteoporosis: 35 mg once a week *or* 5 mg daily
- Treatment of glucocorticoid-induced osteoporosis: 5 mg daily (10 mg daily in postmenopausal women not on hormone replacement therapy)
- Treatment of Paget's disease: 40 mg daily for 6 months
- Renal dosage adjustment: Not recommended in patients with CrCl < 35 ml/min

Risedronate

Brand Name
Actonel, Atelvia

Generic Name
Risedronate

Rx Only

Dosage Form
Tablets

Pregnancy Category C

Dosing
- Treatment and prevention of osteoporosis in postmenopausal women:
  - 5 mg daily or 35 mg once weekly or 150 mg once a month
- Treatment of osteoporosis in males: 35 mg once weekly
- Treatment and prevention of glucocorticoid-induced osteoporosis: 5 mg once daily
- Treatment of Paget's disease: 30 mg once daily for 2 months. Retreatment may be necessary after 2 months of observation.
- Renal dosage adjustment: Not recommended in patients with CrCl < 30 ml/min

Ibandronate

Brand Name
Boniva

Generic Name
Ibandronate

Rx Only

Dosage Forms
Tablet, injection

Usage
Treatment and prevention of osteoporosis, hypercalcemia of malignancy, metastatic bone disease

Pregnancy Category C

Dosing
- Treatment of postmenopausal osteoporosis:
  - Oral: 150 mg once a month
  - IV: 3 mg every 3 months
- Prevention of postmenopausal osteoporosis: 150 mg PO once a month
- Hypercalcemia of malignancy (unlabeled use): 2–6 mg IV over 1 to 2 hours
- Metastatic bone disease: 6 mg IV every 3 to 4 weeks
- Renal dosage adjustment: Avoid in CrCl < 30 ml/min

Zoledronic Acid

Brand Names
Zometa, Reclast

Generic Name
Zoledronic acid

Rx Only

Dosage Form
Injection

Pregnancy Category D

Dosing
- Treatment of osteoporosis: Reclast 5 mg IV once a year

- Prevention of osteoporosis: Reclast 5 mg IV every 2 years
- Treatment of Paget's disease: Reclast 5 mg IV given as a single dose (no data on retreatment)
- Hypercalcemia of malignancy: Zometa 4 mg IV given as a single dose (may consider retreatment after 7 days)
- Multiple myeloma or metastatic bone disease from solid tumors: Zometa 4 mg IV every 3 to 4 weeks
- Renal dosage adjustment: Not recommended in patients with CrCl < 35 ml/min for Reclast or < 30 ml/min for Zometa

CALCITONIN-SALMON

Introduction

Calcitonin-salmon is a synthetic version of the hormone calcitonin found in salmon, which is ironically more active in humans than human calcitonin. Calcitonin is used for treating postmenopausal osteoporosis, Paget's disease, and hypercalcemia. It is most commonly given intranasally. Calcitonin is less effective than bisphosphonates for the treatment of osteoporosis. It is, therefore, usually considered as third-line therapy.

Mechanism of Action for the Drug Class

Directly inhibits osteoclastic bone resorption; promotes the renal excretion of calcium, phosphate, sodium, magnesium, and potassium by decreasing tubular reabsorption. This drug also increases the jejunal secretion of water, sodium, potassium, and chloride.

Members of the Drug Class

In this section: Calcitonin-salmon

◉ Calcitonin-salmon

Brand Names

Miacalcin, Fortical

Generic Name

Calcitonin-salmon

Rx Only

Dosage Forms

Solution (intranasal spray), injection

Usage

Osteoporosis, treatment of Paget's disease, hypercalcemia

Pregnancy Category C

Dosing

- Treatment of osteoporosis in postmenopausal women:
  - Intranasal: 1 spray per day (200 units) in one nostril; alternate nostrils daily or
  - IM or SubQ: 100 units daily
- Treatment of Paget's disease:
  - IM or SUB-Q: 100 units daily (it is recommended to limit therapy to < 3 months)
- Treatment of hypercalcemia:
  - Initial IM or SUB-Q: 4 units/kg every 12 hours for 1 to 2 days
  - Maximum IM or SUB-Q: 8 units/kg every 6 hours

Adverse Reactions: Most Common

Allergic reactions, nasal mucosal alterations, rhinitis

Adverse Reactions: Rare/Severe/Important

Epistaxis, sinusitis, hypocalcemia, malignancy

Counseling Points (nasal spray)

- Allow the medication to reach room temperature before priming or using a new bottle
- To prime the pump, hold the bottle upright and press the two white side arms of the pump toward the bottle until a full spray is produced
- To administer the medication, place the nozzle into the nostril with the head in the upright position
- The pump should not be primed before each dose
- Take supplemental calcium and vitamin D if dietary intake is inadequate
- Store new unassembled bottles in the refrigerator
- Once the pump has been activated, store bottle at room temperature in an upright position for up to 35 days

Key Points

- Usually used for the treatment of osteoporosis when bisphosphonates are not tolerated
- Patient instructions on how to administer the nasal spray are important to ensure appropriate administration

SEX HORMONES: ESTROGENS, PROGESTINS, ESTROGEN AND PROGESTIN COMBINATIONS

Introduction

These medications are mainly used for the treatment of vasomotor symptoms associated with menopause and the prevention of osteoporosis. However, their use has decreased since the Women's Health Initiative (WHI) trial in 2002. That trial was terminated prematurely because of an increased risk of coronary heart disease and thromboembolic events in patients receiving the combination of estrogen and progesterone. The interpretation of the study has been controversial based on the risk profile of the women included in the study, but it led to a significant decrease in the use of these drugs.

Mechanism of Action for the Drug Class

Estrogens (estradiol, conjugated estrogen, esterified estrogen) are important in developing and maintaining the female reproductive system and secondary sex characteristics, promoting growth and development of the vagina, uterus, fallopian tubes, and breasts. Estrogens are also involved in shaping the skeleton and inhibiting bone resorption. Progestins (medroxyprogesterone) inhibit the secretion of gonadotropins, which, in turn, prevent follicular maturation and ovulation and result in endometrial thinning.

Adverse Reactions for the Drug Class: Most Common

- Estrogen-containing products: Vaginal bleeding, breast tenderness, nausea and vomiting
- Progestin-containing products: Breakthrough bleeding, nausea

Adverse Reactions for the Drug Class: Rare/Severe/Important

- Estrogen-containing products: Weight gain, edema, headache, migraines
- Progestin-containing products: Insomnia, somnolence, weight gain

Contraindications for the Drug Class

Known or suspected pregnancy; undiagnosed abnormal vaginal bleeding; known or suspected breast cancer, except for selected patients treated for metastatic disease; active thromboembolic disorders; severe liver disease

Counseling Points for the Drug Class

- Estrogens have been reported to increase the risk of endometrial carcinoma in postmenopausal women
- Do not use estrogens with or without progestins to prevent heart disease, heart attacks, or strokes
- Do not use estrogens and progestins during pregnancy
- Notify a healthcare provider if any of the following occur: pain in the groin or calves, sharp chest pain or sudden shortness of breath, abnormal vaginal bleeding, missed menstrual period, lumps in the breast, sudden severe headache, vision or speech disturbance, weakness or numbness in an arm or leg, severe abdominal pain, yellowing of the skin or eyes, or severe depression
- Women with an intact uterus should also receive monthly progestins, not estrogen-only products
- While taking estrogens, you should visit your doctor at least once a year for appropriate follow-up

Key Points for the Drug Class

- **Black Box Warnings:**
  - Increased risk of invasive breast cancer was observed in postmenopausal women using conjugated estrogens in combination with medroxyprogesterone
  - Estrogens with or without progestin should not be used to prevent dementia or cardiovascular disease and should be used for the shortest duration possible at the lowest effective dose. The use of unopposed estrogen in women with a uterus is associated with an increased risk of endometrial cancer. Breast budding and breast masses in prepubertal females and gynecomastia and breast masses in prepubertal males have been reported following unintentional contact with application sites of women using topical estradiol (Evamist). Patients should strictly adhere to instructions for use in order to prevent secondary exposure.

Members of the Drug Class (Estrogens)

In this section: Estradiol, estradiol transdermal system (patch), conjugated estrogen

Others: Esterified estrogens, estrone, estropipate, other estradiol formulations (gel, oil)

Major Drug Interactions for the Drug Class

Drugs Affecting Estrogen

Barbiturates, rifampin, phenytoin, carbamazepine, and other agents that induce hepatic microsomal enzymes (CYP3A4): May lower estrogen levels

Estrogen's Effect on Other Drugs

Corticosteroids: May increase the pharmacologic and toxicologic effects

◉ Estradiol

Brand Name

Estrace

Generic Name
Estradiol

Rx Only

Dosage Form
Tablet

Usage
Treatment of moderate-to-severe vasomotor symptoms, vulvar and vaginal atrophy associated with menopause, female hypoestrogenism, breast cancer (palliation only), androgen-dependent carcinoma of the prostate, *prevention of osteoporosis*, abnormal uterine bleeding due to hormonal imbalance

Pregnancy Category X

Dosing
- Treatment of moderate to severe vasomotor symptoms, vulvar and vaginal atrophy associated with menopause:
  - Initial dose: 1–2 mg daily adjusted to control symptoms
  - Administration should be cyclic, 3 weeks on, 1 week off
  - Discontinuation/tapering: Attempts to discontinue or taper should be considered at 3- to 6-month intervals
- Treatment of female hypoestrogenism: Initial dose of 1–2 mg daily adjusted to control symptoms
- Treatment of breast cancer for palliation only: Initial dose of 10 mg 3 times daily
- Treatment of advanced androgen-dependent carcinoma of the prostate: Initial dose of 1–2 mg 3 times daily adjusted to control symptoms
- Prevention of osteoporosis: Initial dose of 0.5 mg administered cyclically (23 days on and 5 days off), dose adjusted to control menopausal symptoms

◉ Estradiol Transdermal System (Patch)

Brand Names
Climara, Estraderm, Vivelle-Dot

Generic Name
Estradiol transdermal system

Rx Only

Dosage Form
Patch

Usage
Treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy; prevention of postmenopausal osteoporosis

Pregnancy Category X

Dosing
- Climara: 0.025–0.05 mg/day applied to the skin once weekly, adjusted based on symptoms
- Estraderm: 0.05 mg/day applied to the skin twice weekly, adjusted based on symptoms
- Vivelle-Dot: 0.025–0.05 mg applied to skin twice weekly, adjusted based on symptoms

Counseling Points
Guidelines for applying the transdermal system:
- Place the adhesive side on a clean, dry area of the lower abdomen or the upper quadrant of the buttock. The area selected should not be oily, damaged, or irritated
- Do not apply the transdermal system to the breasts
- Rotate the sites of application
- Press the system firmly in place for at least 10 seconds
- If a system falls off, apply a new one for the remainder of the treatment duration
- Only one system should be worn at a time
- Swimming, bathing, or using a sauna may decrease the adhesion of the system

Key Points
- Mainly used for the treatment of vasomotor symptoms
- In women who are taking oral estrogens, the transdermal system can be initiated 1 week after withdrawal of oral therapy
- Therapy may be given continuously in women who do not have an intact uterus. In patients with an intact uterus, therapy may be given on a cyclic schedule (3 weeks on, 1 week off)
- Climara is a continuous transdermal system for once-weekly administration; Estraderm and Vivelle-Dot are continuous-transdermal systems for twice-weekly administration

◉ Conjugated Estrogens

Brand Name
Premarin

Generic Name
Conjugated estrogens

Rx Only

Dosage Forms
Tablet, injection

Usage
Treatment of moderate-to-severe vasomotor symptoms, prevention of osteoporosis, vulvar and vaginal atrophy, female hypoestrogenism, abnormal uterine bleeding, metastatic breast cancer, advanced prostate cancer

Pregnancy Category

Contraindicated during pregnancy

Dosing

Vasomotor symptoms/vulvar and vaginal atrophy: Oral: 0.3–1.25 mg daily

Key Points

- Mainly used for the treatment of vasomotor symptoms
- Conjugated estrogens may be given continuously with no interruption in therapy or in cyclic regimens (regimens such as 25 days on drug followed by 5 days off)
- Attempts to discontinue or taper medication should be made at 3- to 6-month intervals

Members of the Drug Class (Progestins)

In this section: Medroxyprogesterone
Others: Hydroxyprogesterone, norethindrone acetate, progesterone, megestrol

◉ Medroxyprogesterone

Brand Names

Cycrin, Provera, Depo-Provera, Depo-Sub-Q Provera 104

Generic Name

Medroxyprogesterone

Rx Only

Dosage Forms

Tablet, injection

Usage

Management of endometriosis-associated pain (Depo-Sub-Q Provera only), secondary amenorrhea, abnormal uterine bleeding due to hormonal imbalance, reduction of endometrial hyperplasia in postmenopausal women receiving estrogens, *prevention of pregnancy*

Pregnancy Category X

Dosing

- Management of endometriosis-associated pain: 104 mg SUB-Q every 3 months (13 weeks)
- Secondary amenorrhea: 5 or 10 mg tablets daily for 5 to 10 days
- Abnormal uterine bleeding due to hormonal imbalance: 5 or 10 mg tablets daily for 5 to 10 days beginning on day 16 or day 21 of the menstrual cycle
- Reduction of endometrial hyperplasia in postmenopausal women receiving 0.625 mg of conjugated estrogens: 5 or 10 mg tablets daily for 12 to 14 consecutive days per month, either beginning on day 1 of the menstrual cycle or day 16 of the menstrual cycle
- Prevention of pregnancy:
  - IM injection: 150 mg every 3 months (13 weeks)
  - SUB-Q injection: 104 mg every 3 months (12–14 weeks)

Counseling Points

- Advise patients that at the beginning of Depo-Provera therapy, their menstrual cycle may be disrupted and irregular and unpredictable bleeding or spotting may occur
- Progestin withdrawal bleeding usually occurs within 3 to 7 days after discontinuing oral therapy
- Depo-Sub-Q Provera should be given by SUB-Q injection into the anterior thigh or abdomen

Key Point

Women who use Depo-Provera Contraceptive Injection (IM or SUB-Q) may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible. Depo-Provera Contraceptive Injection should be used as a long-term birth control method (e.g., > 2 years).

◉ Conjugated Estrogen/ Medroxyprogesterone Acetate

Brand Names

Prempro, Premphase

Generic Name

Conjugated estrogen/medroxyprogesterone acetate

Rx Only

Dosage Form

Tablet

Usage

Treatment of moderate-to-severe vasomotor symptoms, vulvar and vaginal atrophy, prevention of postmenopausal osteoporosis

Pregnancy Category

Contraindicated during pregnancy

Dosing

- Prempro: Start with 0.3 mg/1.5 mg, with subsequent dosage adjustments based on patient response and symptoms
- Premphase: 0.625 mg tablet daily on days 1 to 14 and 0.625 mg/5 mg daily on days 15 to 28

Counseling Point

Take as directed by prescriber

Key Point

Among the estrogen and progesterone products, this medication (combination of estrogen and progesterone) is the agent of choice in women with an intact uterus.

COMBINED ORAL CONTRACEPTIVES, MONOPHASIC

Introduction

The administration of combined oral contraceptives is a contraceptive method that includes a combination of an estrogen and a progestin. They inhibit ovulation when taken daily and are the most common form of pharmacologic birth control. **Table 7-1** summarizes the available monophasic combined oral contraceptives.

Mechanism of Action for the Drug Class

The agents deliver a fixed dosage of estrogen and progestin throughout the cycle that inhibits ovulation by suppressing the gonadotropins, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Additionally, alterations in the genital tract, including the cervical mucus, which inhibits sperm penetration, and the endometrium, which reduces the likelihood of implantation, may contribute to contraceptive effectiveness.

Members of the Drug Class

In this section: Combinations of ethinyl estradiol and levonorestrel/norethindrone/desogestrel/drospirenone/norgestimate

Others: Combinations of ethinyl estradiol and ethynodiol or mestranol

Rx Only for the Drug Class

Dosage Form for the Drug Class

Tablet

TABLE 7-1 Combined Oral Contraceptives (Monophasic)

Brand Name	Generic Name and Dosage
Alesse	Levonorgestrel: 0.1 mg Ethinyl estradiol: 20 µg for 21 days
Desogen	Desogestrel: 0.15 mg Ethinyl estradiol: 30 µg for 21 days
Loestrin FE 1/20, Loestrin 24 FE	Norethindrone acetate: 1 mg Ethinyl estradiol: 20 µg for 21 days Ferrous fumarate: 75 mg for 7 days
Ocella	Drospirenone: 3 mg Ethynyl estradiol: 30 µg for 21 days
Lo-Ovral	Norgestrel: 0.3 mg Ethynyl estradiol: 30 µg for 21 days
Ortho-Cyclen	Norgestimate: 0.25 mg Ethynyl estradiol: 35 µg for 21 days
Yasmin	Drospirenone: 3 mg Ethynyl estradiol: 30 µg for 21 days
Yaz	Drospirenone: 3 mg Ethynyl estradiol: 20 µg for 24 days
Seasonale	Levonorgestrel: 0.15 mg Ethynyl estradiol: 30 µg for 48 days

Usage for the Drug Class

Prevention of pregnancy in women, treatment of menorrhagia, pain associated with endometriosis, dysmenorrhea

Pregnancy Category X for the Drug Class

Dosing for the Drug Class

- 21-day regimen: Day 1 of cycle is the first day of menstrual bleeding. Take 1 tablet daily for 21 days, beginning on day 5 of cycle. Then, no tablets are taken for 7 days. Whether bleeding has stopped or not, start a new course of 21 days.
- 24-day regimen: Take 24 days of active pills and 4 days of inert (or iron) tablets on the last 4 days of cycle
- 28-day regimen: To eliminate the need to count the days between cycles, some products contain seven inert or iron-containing tablets to permit continuous daily dosage during the entire 28-day cycle

Adverse Reactions for the Drug Class: Most Common

Nausea, vomiting, bloating, migraine headaches, edema, breast tenderness, breakthrough bleeding (most often in first few cycles of pills), change in menstrual flow, weight gain, tiredness, fatigue, depression

Adverse Reactions for the Drug Class: Rare/Severe/Important

Myocardial infarction, thromboembolism, cerebral hemorrhage, hypertension, gallbladder disease

Major Drug Interactions for the Drug Class

Drugs Affecting Combined Oral Contraceptives

- Antibiotics: Menstrual irregularities and possible contraceptive failure
- Barbiturates, carbamazepine, griseofulvin, phenytoin, rifampin, protease inhibitors: Decreased efficacy via metabolic induction

Combined Oral Contraceptives' Effects on Other Drugs

- Tricyclic antidepressants, beta blockers, theophylline, benzodiazepines: Increase effect via decreased metabolism

Contraindications for the Drug Class

History of myocardial infarction, coronary artery disease, known or suspected breast carcinoma or estrogen-dependent neoplasm, hepatic adenomas/carcinomas, undiagnosed abnormal genital bleeding, thromboembolic disorder, pregnancy, acute liver disease, women > 35 who smoke

Counseling Points for the Drug Class

- Take oral contraceptive pills at exactly the same time every day for maximum effectiveness and do not exceed dosing intervals > 24 hours
- Missing pills may reduce the effectiveness of the birth control pills and cause spotting or light bleeding

- Continue to take pills throughout all bleeding episodes
- Use an additional method of birth control for the first week of pills during the initial cycle of oral contraceptive pills
- Spotting or breakthrough bleeding may occur during the first few months of therapy. Talk to your healthcare provider if bleeding lasts more than a few days and occurs in more than 1 cycle.
- Notify your healthcare provider if pregnancy is suspected or if any of the following occur: Sudden severe headache, visual disturbances, numbness in an arm or leg, severe abdominal pain, prolonged episodes of bleeding, or amenorrhea
- Appropriate action if 1 or more pills are missed:
  - If 1 pill is missed any time in the cycle, take the pill as soon as you remember and the next pill at its regular time
  - If 2 pills are missed during the first 2 weeks of the cycle, take 2 pills daily for 2 days; then resume taking pills on their regular schedule. Use additional contraception (e.g., condom) for the remainder of the cycle.
  - If 2 pills are missed during the third week of the cycle and you are a day 1 starter, throw out the rest of the pack and start a new pack that same day. If you are a Sunday starter, keep taking 1 pill every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack that same day. Use additional contraception until the new pack of pills is started and for the first 7 days of the new cycle.
  - If 3 or more pills are missed and you are a day 1 starter, throw out the rest of the pack and start a new pack that same day. If you are a Sunday starter, keep taking 1 pill every day until Sunday. On Sunday throw out the rest of the pack and start a new pack that same day. Use additional contraception until the new pack of pills is started and for the first 7 days of the new cycle.

Key Points for the Drug Class

- **Black Box Warning:**
  - The risk of cardiovascular side effects is increased in women who smoke cigarettes; risk increases with age (especially women > 35 years of age) and the number of cigarettes smoked; women who use combination hormonal contraceptives should be strongly advised not to smoke. Use is contraindicated in patients > 35 years of age who smoke.
- Combination oral contraceptives are the most common type of pharmacologic contraception
- Special instructions exist if one or more doses are missed
- Seasonale is a combined oral contraceptive that provides continued estrogen and progesterone for 3 months

COMBINED ORAL CONTRACEPTIVES, BIPHASIC

Mechanism of Action for the Drug Class

These drugs inhibit ovulation (as explained in the monophasic drug class section). In this drug class, the amount of estrogen remains the same for the first 21 days of the cycle and decreases at the end of the cycle.

Members of the Drug Class

In this section: Combinations of ethinyl estradiol and desogestrel
Others: Combinations of ethinyl estradiol and norethindrone

◉ Desogestrel/Ethinyl Estradiol

Brand Name

Mircette

Generic Name

Desogestrel/ethinyl estradiol

Rx Only

Dosage Form

Tablet

Usage

Prevention of pregnancy in women

Pregnancy Category X

Dosing

Desogestrel 0.15 mg/ethinyl estradiol 20 μg for 21 days, placebo for 2 days, and then ethinyl estradiol 10 μg for 5 days

COMBINED ORAL CONTRACEPTIVES, TRIPHASIC

Mechanism of Action for the Drug Class

This drug inhibits ovulation (as explained in the monophasic drug class section). In this drug class, the estrogen amount remains the same or varies throughout the cycle; the progestin amount varies. **Table 7-2** summarizes the available triphasic combined oral contraceptives.

Members of the Drug Class

In this section: Combinations of ethinyl estradiol and levonorgestrel/norethindrone/desogestrel/norgestimate

Dosage Form for the Drug Class

Tablet

Usage for the Drug Class

Prevention of pregnancy in women, treatment of moderate acne vulgaris in women > 15 years old

Pregnancy Category X for the Drug Class

TABLE 7-2 Combined Oral Contraceptives (Triphasic)

Brand Name	Generic Name and Dosage
Ortho-Novum 7/7/7	Norethindrone: 0.5 mg/ethinyl estradiol: 35 µg for 7 days Norethindrone: 0.75 mg/ethinyl estradiol: 35 µg for 7 days Norethindrone: 1 mg/ethinyl estradiol: 35 µg for 7 days
Ortho Tri-Cyclen, TriNessa, Tri-Sprintec	Norethindrone: 0.18 mg/ethinyl estradiol: 35 µg for 7 days Norethindrone: 0.215 mg/ethinyl stradiol: 35 µg for 7 days Norethindrone: 0.25 mg/ethinyl estradiol: 35 µg for 7 days
Ortho Tri-Cyclen-Lo	Norethindrone: 0.5 mg/ethinyl estradiol: 25 µg for 7 days Norethindrone: 0.215 mg/ethinyl estradiol: 25 µg for 7 days Norethindrone: 0.25 mg/ethinyl estradiol: 25 µg for 7 days
Triphasil, Trivora	Norethindrone: 0.5 mg/ethinyl estradiol: 30 µg for 6 days Norethindrone: 0.75 mg/ethinyl estradiol: 40 µg for 5 days Norethindrone: 0.125 mg/ethinyl estradiol: 30 µg for 7 days

ESTROGEN AND PROGESTERONE VAGINAL RING

Mechanism of Action for the Drug Class

The vaginal ring contains the combination of ethinyl estradiol and etonogestrel. It inhibits ovulation by decreasing the amount of gonadotropin hormones, similar to the mechanism of combined oral contraceptives.

Members of the Drug Class

In this section: Ethinyl estradiol and etonogestrel

◉ Ethinyl estradiol 0.015 mg/day and etonogestrel 0.12 mg/day

Brand Name

NuvaRing

Generic Name

Ethinyl estradiol 0.015 mg/day and etonogestrel 0.12 mg/day

Rx Only

Dosage Form

Vaginal ring device

Usage

Contraception

Pregnancy Category

Discontinue if pregnancy occurs

Dosing

Insert one ring vaginally and leave in place for 3 weeks, then remove for 1 week to allow for breakthrough bleeding

Counseling Points

- Administration: Press sides of the ring together between the fingers and insert folded into the vagina. Specific placement is not required
- Do not dispose of the ring in the toilet

- A different contraceptive method should be used if the ring is expelled for > 3 hours. If < 3 hours, it should be washed and reinserted.
- A new ring is inserted 7 days after the last one was removed. It should be inserted at approximately the same time.

Key Points

- **Black Box Warning:**
  - The risk of cardiovascular side effects is increased in women who smoke cigarettes; risk increases with age (especially women > 35 years of age) and the number of cigarettes smoked; women who use combination hormonal contraceptives should be strongly advised not to smoke. Use is contraindicated in patients > 35 years of age who smoke.
- The efficacy of the vaginal ring is similar to that of combined oral contraceptives
- Side effects and precautions are the same as for combined oral contraceptives
- May have the advantage of better compliance

PROGESTIN-ONLY ORAL CONTRACEPTIVES

Mechanism of Action for the Drug Class

Progestins prevent conception by thickening the cervical mucus to inhibit sperm penetration, lower the midcycle LH and FSH peaks, slow the movement of the ovum through the fallopian tubes, and alter the endometrium. In approximately 50% of users, they also suppress ovulation.

Members of the Drug Class

In this section: Norethindrone
Others: Norgestrel, etonogestrel

◉ Norethindrone

Brand Name

Micronor

Generic Name

Norethindrone

Rx Only

Dosage Form

Tablet

Usage

Contraception, abnormal uterine bleeding, and amenorrhea

Dosing

Contraception: 0.35 mg daily
Abnormal uterine bleeding and amenorrhea: 2.5–10 mg daily for 5 to 10 days

Pregnancy Category X

Counseling Points

- Use a backup nonpharmacologic method of contraception (such as condoms) for the next 48 hours whenever pills are taken ≥ 3 hours late
- Appropriate action if 1 or more progestin-only pills are missed:
  - If the pill is taken ≥ 3 hours late, take the pill as soon as remembered and use additional contraception for 48 hours
  - If 1 or more pills are missed, take it as soon as remembered. Take today's pill at its regular time, even if that means taking 2 pills in 1 day. Use additional contraception for 48 hours.

Key Points

- Used for contraception in patients that cannot take estrogen
- Effectiveness may be reduced dramatically when progestin-only pills are taken > 3 hours late

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Introduction

Raloxifene is the most commonly used medication in the family of selective estrogen receptor modulators (SERMs). It is more selective in its action than tamoxifen (which is discussed in Chapter 4) and is used in the treatment of osteoporosis and in the prevention of breast cancer in high-risk women. Note that it is not as effective as bisphosphonates for the treatment and prevention of osteoporosis.

Mechanism of Action for the Drug Class

These agents are mixed estrogen agonist/antagonists, with estrogenic agonist action in bones and estrogenic antagonistic action in breast and uterine tissue. They inhibit bone resorption and reduce biochemical markers of bone turnover.

Members of the Drug Class

In this section: Raloxifene
Others: Tamoxifen, ospemifene, toremifene

◉ Raloxifene

Brand Name

Evista

Generic Name

Raloxifene

Rx Only

Dosage Form

Tablet

Usage

Prevention and treatment of postmenopausal osteoporosis, risk reduction for invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women with high risk for invasive breast cancer

Pregnancy Category X

Dosing

- 60 mg daily
- Renal dosage adjustment: In cases of moderate to severe renal dysfunction, the dose may be reduced. However, the safety and efficacy in such patients have not been established.
- Hepatic dosage adjustment: Dose may be reduced in cases of hepatic dysfunction. However, safety and efficacy in such patients have not been established.

Adverse Reactions: Most Common

Hot flashes, nausea

Adverse Reactions: Rare/Severe/Important

Muscle aches, vaginal bleeding, abdominal pain, thromboembolism

Major Drug Interactions

Drugs Affecting Raloxifene

- Cholestyramine: Reduces raloxifene absorption

Raloxifene's Effect on Other Drugs

- Levothyroxine: Decreases absorption
- Warfarin: May decrease prothrombin time by 10%

Contraindications

Women who are or may become pregnant; history of venous thromboembolic events

Counseling Points

- Discontinue raloxifene at least 72 hours prior to and during prolonged immobilization to prevent clot formations
- Avoid prolonged restrictions of movement during travel because of the increased risk of blood clots
- Take supplemental calcium and vitamin D if daily intake is inadequate

Key Points

- **Black Box Warning:**
  - Raloxifene may increase the risk for DVT and PE; use is contraindicated in patients with history of or current venous thromboembolic disorders. The risk of death due to stroke is increased in postmenopausal women with coronary heart disease or at increased risk for major coronary events.
- Used for the prevention and treatment of postmenopausal osteoporosis and for the prevention of breast cancer in high-risk women

GLUCOCORTICOIDS

Introduction

Glucocorticoids are anti-inflammatory, immunosuppressant agents used in the treatment of a variety of diseases, including those of allergic, dermatologic, endocrine, hematologic, inflammatory, neoplastic, nervous system, renal, respiratory, rheumatic, and autoimmune origin. They may be used in the management of cerebral edema and chronic swelling; as a diagnostic agent, such as in the case of Cushing's syndrome; as an antiemetic; and for many other uses. They have significant adverse effects that can be dose and duration limiting. Converting from one glucocorticoid to another is a common practice. Approximate conversions are listed in **Table 7-3**.

Mechanism of Action for the Drug Class

The exact mechanism of glucocorticoids is unknown. They inhibit interleukin-1 and various other cytokines that mediate inflammatory responses. They also decrease

TABLE 7-3 Glucocorticoid Conversion

Glucocorticoid	Equivalent Anti-Inflammatory Dose
Cortisone	25 mg
Hydrocortisone	20 mg
Prednisone	5 mg
Prednisolone	5 mg
Methylprednisolone	4 mg
Triamcinolone	4 mg
Betamethasone	0.75 mg
Dexamethasone	0.75 mg

inflammation by suppressing migration of polymorphonuclear leukocytes and decreasing capillary permeability.

Members of the Drug Class

In this section: Methylprednisolone and prednisone, dexamethasone

Others: Betamethasone, cortisone, hydrocortisone, prednisolone, triamcinolone (these are other systemic glucocorticoids)

Usage for the Drug Class

Treatment of multiple inflammatory conditions; *acute asthma*; rheumatoid arthritis (RA); dermatologic lesions, such as keloids; autoimmune disorders, such as multiple sclerosis; adrenogenital syndrome; adjunctive therapy for *Pneumocystis jiroveci* pneumonia (PCP)

Adverse Reactions for the Drug Class: Most Common

GI irritation, increased appetite, nervousness/restlessness, weight gain, acne, glucose intolerance (transient), lipid abnormalities (transient)

Adverse Reactions for the Drug Class: Rare/Severe/Important

Infections, adrenal suppression, rounding out of the face, hirsutism, glaucoma, osteoporosis, peptic ulceration

Major Drug Interactions for the Drug Class

Drugs Affecting Glucocorticoids

- Alcohol/NSAIDs: Increase risk of gastric ulceration
- Estrogens: May increase toxicity

Glucocorticoids' Effects on Other Drugs

- Insulin/oral hypoglycemic agents: Increase glucose levels

Contraindications for the Drug Class

Systemic fungal infections, concomitant administration of live vaccines

Counseling Point for the Drug Class

Take oral tablets with food and preferably in the morning

Key Points for the Drug Class

- Used for many inflammatory conditions
- Too-rapid withdrawal of therapy, especially after prolonged use, may cause acute, possibly life-threatening adrenal insufficiency. If course of therapy is > 10 to 14 days, therapy must be tapered when discontinuing.
- The prescribed dosages of glucocorticoids vary, depending on the compound used and the nature of the patient's condition. Depending on these factors, the dose may be taken once a day, spaced evenly throughout the day, or even taken every other day.

Methylprednisolone and Prednisone

Brand Names

Medrol and Medrol Dosepak, Depo-Medrol, Solu-Medrol

Generic Name

Methylprednisolone

Dosage Forms

Tablet, injection

Brand Names

Deltasone, Orasone

Generic Name

Prednisone

Rx Only

Dosage Forms

Tablet, oral solution

Pregnancy Category C/D

Dosing

- Treatment of acute asthma, including status asthmaticus and allergic rhinitis:
  - Oral: 4–48 mg/day (methylprednisolone) or 40–60 mg/day (prednisone) for 3 to 10 days; individualize dose based on response
  - Alternate-day oral therapy: Twice the daily dose may be administered every other day
  - Dosepak: Taper each day according to manufacturer's instructions (6-day therapy starting with 24 mg day 1; decrease by 4 mg every day; and finish with 4 mg on day 6)
  - IV (sodium succinate): Loading dose: 2 mg/kg/dose then 0.5: 1 mg/kg/dose every 6 hours for 5 days
- Treatment of rheumatoid arthritis:
  - Intra-articular (acetate):
    - Large joints (such as knees and ankles): 20–80 mg
    - Medium joints (such as elbows and wrists): 10–40 mg
    - Small joints (such as metacarpophalangeal): 4–10 mg
  - Oral: < 10 mg/day

- Dermatologic lesions (chronic): 40–120 mg IM (acetate) weekly
- Anti-inflammatory or immunosuppression: 10–40 mg daily oral or IV (sodium succinate) in divided doses
- Acute exacerbation of multiple sclerosis:
  - IV: 500–1000 mg daily for 3 to 5 days, with or without a short prednisone taper
  - Oral: 200 mg (prednisone) daily for 1 week then 80 mg every other day for 1 month

⦿ Dexamethasone

Brand Names
Decadron, DexPak

Generic Name
Dexamethasone

Rx Only

Dosage Forms
Tablet, oral solution, injection

Usage
Treatment of a variety of diseases, including those of allergic, dermatologic, endocrine, hematologic, inflammatory, neoplastic, nervous system, renal, respiratory, rheumatic, and autoimmune origin; management of cerebral edema and chronic inflammation; diagnosis of Cushing's syndrome; antiemetic

Pregnancy Category C

Dosing
- Anti-inflammatory:
  - Oral, IM, IV: 0.75–9 mg daily in divided doses every 6 to 12 hours
  - Intra-articular, intralesional, or soft tissue: 0.4–6 mg daily
- Cerebral edema: 10 mg IV stat, then 4 mg IM/IV (should be given as sodium phosphate) every 6 hours until response is maximized

PARATHYROID HORMONE ANALOGS

Introduction
Teriparatide is a recombinant form of parathyroid hormone. It has been shown to decrease osteoporosis fractures. This agent is usually reserved for severe osteoporosis or for patients who are intolerant of bisphosphonates.

Mechanism of Action for the Drug Class
As a parathyroid hormone agonist, it stimulates osteoblast function, increases calcium absorption from the GI tract, and increases calcium reabsorption from the kidneys

Members of the Drug Class
In this section: Teriparatide

⦿ Teriparatide

Brand Name
Forteo

Generic Name
Teriparatide

Rx Only

Dosage Form
Injection

Usage
Osteoporosis, glucocorticoid-induced osteoporosis

Pregnancy Category C

Dosing
20 mg SUB-Q daily

Adverse Reactions: Most Common
Transient hypercalcemia

Adverse Reactions: Rare/Severe/Important
Osteosarcomas, orthostatic hypotension

Major Drug Interactions
No known significant interactions

Counseling Points
- The prefilled pen needs to be kept refrigerated
- Inject subcutaneously in the thigh or abdomen. Patients may need to be shown how to do this.

Key Points
- **Black Box Warning:**
  - In animal studies, teriparatide has been associated with an increase in osteosarcoma; risk was dependent on both dose and duration. Avoid use in patients with an increased risk of osteosarcoma (Paget disease, prior radiation, unexplained

elevation of alkaline phosphatase, prior external beam or implant radiation therapy involving the skeleton, or in patients with open epiphyses.
- Because of its significant cost, subcutaneous administration, and limited long-term safety data, teriparatide is reserved for patients with severe osteoporosis and for those intolerant to bisphosphonates
- Administration of teriparatide needs to be combined with calcium and vitamin D supplements

THYROID HORMONES

Introduction

Thyroid hormones are chemical compounds that are essential for the function of every cell in the body. They help regulate growth and the body's metabolism. The two most important thyroid hormones are thyroxine (T4) and tri-iodothyronine (T3).

Mechanism of Action for the Drug Class

The effect of thyroid hormones is believed to be exerted through control of DNA transcription and protein synthesis. Their principal effect is to increase the metabolic rate of body tissues, as noted by increased respiratory rate; cardiac output; heart rate; and protein, fat, and carbohydrate metabolism. They exert a profound effect on every organ system, particularly CNS development. Levothyroxine is a synthetic form of T4.

Members of the Drug Class

In this section: Levothyroxine sodium
Others: Liothyronine, liotrix, thyroid (desiccated)

◉ Levothyroxine Sodium

Brand Names

Levothroid, Levoxyl, Synthroid, Unithroid, Tirosint

Generic Name

Levothyroxine sodium

Dosage

Rx Only

Dosage Forms

Tablet, injection

Usage

Hypothyroidism, myxedema coma

Pregnancy Category A

Dosing

- Hypothyroidism:
  - Oral: 100–125 µg daily
  - Initial dose in patients > 50 years old or with underlying cardiac disease: 25–50 µg daily
  - Maximum dose: 300 µg daily
- Myxedema coma:
  - Initial dose: 300–500 µg IV, followed by 50–100 µg daily until patient can be switched to the oral formulation

Adverse Reactions: Most Common

Fatigue, increased appetite, weight loss, heat intolerance, hyperhidrosis

Adverse Reactions: Rare/Severe/Important

Hair loss, menstrual irregularities, nervousness, irritability, insomnia

Major Drug Interactions

Drugs Affecting Levothyroxine

- Cholestyramine: Impairs absorption
- Estrogens: Increase serum thyroxine-binding globulin, thus decreasing free thyroxine concentrations
- Iron and calcium: Decrease absorption (separate administration)
- Raloxifene: Decreases absorption

Levothyroxine's Effect on Other Drugs

- Warfarin: Increased prothrombin time/international normalized ratio

Essential Monitoring Parameters

Thyroid-stimulating hormone, T3, and T4 blood concentrations should be obtained every 6 to 8 weeks initially until stable, every 8 to 12 weeks after dose adjustments, and annually thereafter

Contraindications

Untreated thyrotoxicosis, uncorrected adrenal insufficiency

Counseling Points

- Report any signs and symptoms of thyroid hormone toxicity, such as chest pain, increased pulse rate, palpitations, excessive sweating, heat intolerance, and nervousness

- Take oral tablets first thing in the morning on an empty stomach at least a half hour before any other food
- If receiving concomitant therapy with cholestyramine and levothyroxine, take doses at least 4 to 5 hours apart

Key Points

- **Black Box Warning:**
  - Thyroid supplements are ineffective and potentially toxic when used for the treatment of obesity or for weight reduction
- Most commonly used medication for the treatment of hypothyroidism
- Doses should be adjusted in 12.5–25 µg increments
- In patients >50 years old with cardiac disease, lower doses should be used for initial doses and titration

REVIEW QUESTIONS

1. Which of the following statements about NuvaRing is correct?
   - a. It is a progesterone only product
   - b. It needs to be left in place for 3 weeks
   - c. It needs to be left in place for 1 week
   - d. The ring should be disposed of in the toilet

2. All of the following are common side effects of Actonel except?
   - a. Hypocalcemia
   - b. Hypercalcemia
   - c. Abdominal pain
   - d. Nausea

3. Which of the following is an appropriate dose of alendronate for the treatment of osteoporosis?
   - a. 5 mg daily
   - b. 70 mg weekly
   - c. 35 mg weekly
   - d. Both A and C

4. Which of the following medications interact with Ortho-Tri-Cyclen?
   - a. Rifampin
   - b. Phenytoin
   - c. Carbamazepine
   - d. All of the above

5. Which of the following is an example of a monophasic combined oral contraceptive?
   - a. Yaz
   - b. Triphasil
   - c. Mircette
   - d. Ortho-Novum 7/7/7

6. All of the following statements about Forteo are true except:
   - a. Used for the treatment of osteoporosis
   - b. Given subcutaneously
   - c. It is a synthetic thyroid hormone
   - d. Transient hypercalcemia is common

7. Which of the following medications will decrease the absorption of Synthroid?
   - a. Metoprolol
   - b. Iron
   - c. Penicillin
   - d. Warfarin

8. Which of the following statements about levothyroxine is correct?
   - a. It is available only as a tablet
   - b. Weight gain is a common adverse effect
   - c. It is used for the treatment of myxedema coma
   - d. It should be taken with antacids to increase absorption

9. When should we evaluate thyroid levels (TSH, T4, T3) after Synthroid is started?
   - a. 5 to 7 days
   - b. 1 to 2 weeks
   - c. 6 to 8 weeks
   - d. Every 6 months

10. How often is Reclast given for the treatment of osteoporosis?
    - a. Every month
    - b. Every 6 months
    - c. Every year
    - d. Reclast is not indicated for the treatment of osteoporosis

11. All of the following statements about Calcitonin are correct except?

- **a.** It is considered first line for the treatment of osteoporosis
- **b.** It is available as an intranasal spray and injection
- **c.** It is used in the treatment of Paget's disease
- **d.** It directly inhibits osteoclastic bone resorption

12. All of the following medications are indicated for the treatment of vasomotor symptoms in postmenopausal women except?

- **a.** Premarin
- **b.** Prempro
- **c.** Depo-Provera
- **d.** Climara

13. All of the following are indications for the use of Seasonale except?

- **a.** Prevention of pregnancy
- **b.** Treatment of vasomotor symptoms
- **c.** Treatment of dysmenorrhea
- **d.** Treatment of menorrhagia

14. All of the following statements about Evista are true except:

- **a.** Normal dose is 60 mg daily
- **b.** Used for the prevention of osteoporosis
- **c.** Patient should take calcium and vitamin D supplements if daily intake is inadequate while on the medication
- **d.** A common adverse effect is fluid retention

15. What type of contraceptive is Micronor?

- **a.** Monophasic combined oral contraceptive
- **b.** Biphasic combined oral contraceptive
- **c.** Progestin-only contraceptive
- **d.** Estrogen-only contraceptive

16. Which of the following glucocorticoids is (are) available as an injection?

- **a.** Prednisone
- **b.** Methylprednisolone
- **c.** Dexamethasone
- **d.** B and C are correct

17. Which of the following is (are) adverse effects of Depo-Provera?

- **a.** Decrease in bone mineral density
- **b.** Breakthrough bleeding
- **c.** Nausea
- **d.** All of the above

18. All of the following are estradiol formulation except?

- **a.** Estrace
- **b.** Estraderm
- **c.** Megace
- **d.** Vivelle-Dot

19. What is the interaction between warfarin and levothyroxine?

- **a.** Levothyroxine increases warfarin anticoagulation effects
- **b.** Warfarin decreases levothyroxine concentrations
- **c.** Warfarin increases levothyroxine concentrations
- **d.** There is no interaction between warfarin and levothyroxine

20. All of the following statements about Climara are correct except?

- **a.** Should be applied to the breast area once a week
- **b.** Using a sauna may decrease Climara's efficacy
- **c.** Indicated for the treatment of vasomotor symptoms
- **d.** Rotate the sites of application

21. All of the following are indications for the use of glucocorticoids except?

- **a.** Acute asthma
- **b.** Status epilepticus
- **c.** Allergic rhinitis
- **d.** Rheumatoid arthritis

22. Premarin is indicated for all of the following conditions except?

- **a.** Vulvar and vaginal atrophy
- **b.** Female hypoestrogenism
- **c.** Contraception
- **d.** Prevention of osteoporosis

23. All of the following are true about glucocorticoids except?

- **a.** Can increase glucose concentrations
- **b.** Dexamethasone is more potent than methylprednisolone
- **c.** GI irritation is a common adverse effect
- **d.** Prednisone is more potent that methylprednisolone

24. All of the following are common adverse effects of Solu-Medrol except?

- **a.** Drowsiness
- **b.** Increased appetite
- **c.** Nervousness/restlessness
- **d.** Acne

25. All of the following are important counseling points about the use of combined oral contraceptives except?

- **a.** Take at exactly the same time every day for maximum effectiveness
- **b.** Missing pills may cause spotting or light bleeding
- **c.** If one dose is missed a new package needs to be started
- **d.** Spotting or breakthrough bleeding may occur during the first few months of therapy

26. All of the following are important counseling points for Fosamax except?

- **a.** Take with food first thing in the morning
- **b.** Notify your physician if new symptoms of heartburn or difficulty swallowing appear
- **c.** Do not lie down for 30 minutes after taking the medication
- **d.** Take supplemental calcium and vitamin D if dietary intake is inadequate

27. Which of the following is a contraindication to raloxifene?

- **a.** Hypersensitivity to sulfa
- **b.** History of thromboembolism
- **c.** History of diabetes mellitus
- **d.** History of hypertension

28. Which of the following medications has been associated with an increased risk of osteosarcoma?

- **a.** Raloxifene
- **b.** Levothyroxine
- **c.** Teriparatide
- **d.** Dexamethasone

29. All of the following are Black Box Warnings for the use of estrogen and conjugated estrogens except?

- **a.** Increased risk of invasive breast cancer was observed in postmenopausal women using conjugated estrogens (CE) in combination with medroxyprogesterone acetate (MPA)
- **b.** Estrogens with or without progestin should not be used to prevent dementia
- **c.** The use of unopposed estrogen in women with a uterus is associated with an increased risk of skin cancer
- **d.** Estrogens with or without progestin should not be used to prevent cardiovascular disease

30. How many days of therapy are in a Medrol-Dosepak?

- **a.** 3
- **b.** 6
- **c.** 9
- **d.** 12

CHAPTER 8

Gastrointestinal Agents

Lawrence Carey, PharmD

5-HT$_3$ RECEPTOR ANTAGONISTS

Introduction

Serotonin subtype-3 (5-HT$_3$) receptor antagonists are commonly used in the treatment of nausea and vomiting caused by moderate to highly emetogenic chemotherapy regimens, radiation therapy, and postoperative situations. They are frequently given in combination with one or more additional agents and are most effective when used on a scheduled basis to prevent nausea and vomiting, rather than as needed, or "prn." With the exception of palonosetron, which differs from the other drugs in this class by having a longer half-life and stronger receptor affinity, these agents have not been consistently effective in preventing delayed chemotherapy-induced nausea and vomiting. Of note, alosetron is only indicated for the treatment of severe diarrhea-predominant irritable bowel syndrome (IBS) in women who have chronic IBS symptoms; this agent should not be used for antiemetic purposes.

Mechanism of Action for the Drug Class

Act as a selective antagonist of serotonin subtype-3 (5-HT$_3$) receptors that are present peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the brain. Drugs in this class bind to the 5-HT$_3$ receptors, blocking the signal to the vomiting center in the brain, thus preventing nausea and vomiting.

Members of the Drug Class

In this section: Ondansetron, palonosetron
Others: Alosetron, dolasetron, granisetron

⦿ Ondansetron

Brand Names

Zofran, Zofran ODT, Zuplenz

Generic Name

Ondansetron

Rx Only

Dosage Forms

Injection, oral solution, tablet, orally disintegrating tablet (ODT), oral soluble film

Usage

Prevention of chemotherapy-induced nausea and vomiting, prevention of radiation-induced nausea and vomiting, prevention and treatment of postoperative nausea and vomiting, hyperemesis gravidarum

Pregnancy Category B

Dosing

- Prevention of chemotherapy-induced nausea and vomiting:
  - IV: 0.15 mg/kg/dose (maximum of 16 mg) over 15 minutes for 3 doses, beginning 30 minutes prior to chemotherapy, followed by subsequent doses 4 and 8 hours after the first dose
  - Oral: 24 mg given 30 minutes prior to chemotherapy or 8 mg 30 minutes prior to chemotherapy and repeat in 8 hours, then 8 mg every 12 hours for 1 to 2 days postchemotherapy (dosing regimen dependent on chemotherapy emetogenic potential)
- Prevention of radiation-induced nausea and vomiting: 8 mg orally 1 to 2 hours prior to radiotherapy; may repeat every 8 hours after radiotherapy for 1 to 2 days after completion of radiotherapy
- Prevention of postoperative nausea and vomiting:
  - IV, IM: 4 mg as an undiluted single dose (over 2 to 5 minutes if giving IV) administered immediately before induction of anesthesia or postoperatively if patient experiences nausea and/or vomiting shortly after surgery
  - Oral: 16 mg given 1 hour before induction of anesthesia
- Hyperemesis gravidarum:
  - Oral: 8 mg every 12 hours
  - IV: 10 mg administered over 15 minutes every 8 hours as needed.
- Hepatic dosage adjustment: For Child-Pugh Class C, maximum daily dose of 8 mg (IV and PO)

Adverse Reactions: Most Common

Headache, constipation, dizziness, malaise/fatigue, drowsiness, itching

Adverse Reactions: Rare/Severe/Important

EKG changes (QT prolongation, tachycardia, bradycardia), hypotension, elevated liver function tests

Major Drug Interactions

Ondansetron's Effect on Other Drugs

- Apomorphine: Enhances hypotensive effect
- Additive effect on QT prolongation when combined with other agents known to prolong the QT interval

Contraindications

Concomitant use of apomorphine

Essential Monitoring Parameters

EKG in patients with electrolyte abnormalities, heart failure, bradyarrhythmias, or with concomitant use of QT prolonging medication(s)

Counseling Points

- Do not remove the ODT from the blister pack until you are ready to take the medication. Peel the backing off; do not push through the backing. Using dry hands, place the tablet on the tongue and swallow with saliva.
- Do not remove the orally disintegrating film from the package until immediately before use. Using dry hands, place the film on top of the tongue and allow it to dissolve; swallow with or without liquid.

Key Points

- 5-HT_3 receptor antagonists are frequently used in combination with one or more agents to prevent chemotherapy-associated nausea and vomiting
- In general, the 5-HT_3 receptor antagonists should be taken on a scheduled basis and not as needed because they are more effective in prevention of nausea and vomiting than in treatment of existing symptoms
- Some agents, particularly dolasetron, have been associated with a dose-dependent increase in EKG intervals (PR, QRS, QT/QT_c). In patients with underlying QT prolongation, electrolyte imbalances, or those taking medications known to prolong the QT interval, this could result in torsades de pointes. All 5-HT_3 receptor antagonists should be used with caution in patients at risk.

◉ Palonosetron

Brand Name

Aloxi

Generic Name

Palonosetron

Rx Only

Dosage Form

Injection

Usage

Prevention of chemotherapy-induced nausea and vomiting (including highly emetogenic therapy and acute or delayed moderately emetogenic therapy), prevention and treatment of postoperative nausea and vomiting

Pregnancy Category B

Dosing

- Prevention of chemotherapy-induced nausea and vomiting: 0.25 mg IV over 30 seconds given 30 minutes prior to the start of chemotherapy
- Prevention of postoperative nausea and vomiting: 0.075 mg IV over 10 seconds given immediately prior to anesthesia induction

Adverse Reactions: Most Common

Headache, dizziness, constipation, weakness, anxiety, hyperkalemia

Adverse Reactions: Rare/Severe/Important

EKG changes (QT prolongation, tachycardia, bradycardia), hypotension

Major Drug Interactions

Palonosetron's Effect on Other Drugs

- Apomorphine: Enhances hypotensive effect
- Additive effect on QT prolongation when combined with other agents known to prolong the QT interval

Key Points

- 5-HT_3 receptor antagonists are frequently used in combination with one or more agents to prevent chemotherapy-associated nausea and vomiting. Due to its long half-life, palonosetron is the only 5-HT_3 antagonist that is effective for delayed nausea and vomiting.
- In general, the 5-HT_3 receptor antagonists should be taken on a scheduled basis and not as needed because they are more effective in prevention of nausea and vomiting than treatment of existing symptoms
- Some agents, particularly dolasetron, have been associated with a dose-dependent increase in EKG intervals (PR, QRS, QT/QT_c). In patients with underlying QT prolongation, electrolyte imbalances, or those taking medications known to prolong the QT interval, this could result in torsades de pointes. All 5-HT_3 antagonists should be used with caution in patients at risk.

ANTACIDS

Introduction

The class of antacid agents encompasses a variety of aluminum, magnesium, and calcium products generally used to neutralize gastric acidity. Drugs in this class are available as single and combination therapy preparations in multiple dosage forms, including liquids, Gelcaps, tablets, and chewable tablets. Most of these preparations are available over the counter; therefore, healthcare providers should pay particular attention to the use of these products in patients with renal dysfunction, duration of use > 2 weeks, and those taking prescription drugs known to interact with antacid compounds.

Mechanism of Action for the Drug Class

Neutralize gastric acid, inactivate pepsin, and bind bile salts

Members of the Drug Class

In this section: Magnesium hydroxide/aluminum hydroxide (Maalox), calcium carbonate (Tums)
Others: Numerous preparations of single-ingredient or combinations of aluminum hydroxide, magnesium hydroxide, calcium carbonate, and simethicone are available

◉ Magnesium Hydroxide/ Aluminum Hydroxide

Brand Names

Maalox, Alamag, Mag-Al, Mag-Al Plus, Mylanta

Generic Names

Magnesium hydroxide/aluminum hydroxide ± simethicone; chewable products may also contain calcium carbonate

OTC

Dosage Forms

Oral suspension, tablet, chewable tablet

Usage

Acid indigestion, heartburn, short-term treatment of hyperphosphatemia in renal failure; aluminum hydroxide may also be used for the prevention of GI bleeding and as an adjunctive agent in peptic ulcer disease

No Official Pregnancy Category

Dosing

- Oral suspension: 10–20 ml every 4 to 6 hours as needed before meals and at bedtime (see product-specific dosing)
- Tablets/chewable tablets: One to two tablets every 4 to 6 hours as needed before meals and at bedtime (see product-specific dosing)
- Renal dosage adjustment: Use caution; aluminum and magnesium may accumulate (no specific dosing requirements)

Adverse Reactions: Most Common

Constipation, diarrhea, chalky taste, abdominal cramps, nausea, vomiting

Adverse Reactions: Rare/Severe/Important

Hypermagnesemia, aluminum intoxication, hypophosphatemia, metabolic alkalosis, intestinal obstruction, dehydration

Major Drug Interactions

Drugs Affecting Magnesium Hydroxide/Aluminum Hydroxide

Vitamin D analogs: May increase the absorption of aluminum, leading to toxicity

Magnesium Hydroxide/Aluminum Hydroxide's Effect on Other Drugs

Antacid preparations have been reported to decrease the pharmacologic effect/exposure of many drugs when concomitantly administered. Monitor for therapeutic efficacy and failure. Good evidence supports a significant interaction with iron salts, tetracyclines, itraconazole, ketoconazole, rilpivirine, fluoroquinolones, quinine, and thyroid hormones.

Counseling Points

- Separate administration of antacid medications by at least 2 hours from other medications
- Use with caution if you have renal insufficiency. Contact a physician immediately if irregular heartbeat, severe stomach pain, or excessive weakness or tiredness occurs.
- For self-medication, antacids should not be taken for longer than 2 weeks. Contact a physician if symptoms are not relieved promptly or symptoms return often.

Key Points

- Because of easy OTC access to these agents, patients should be assessed for potential drug interactions and renal impairment that may result in toxicity
- Symptoms that recur and persist beyond 2 weeks may be a sign of more serious disease; these patients should be referred to a physician

◉ Calcium Carbonate

Brand Names

Tums, Maalox Chewable, Calci-Chew, Rolaids,

Generic Name

Calcium carbonate

OTC

Dosage Forms

Chewable tablet, gum tablet, lozenge, liquid

Usage

Acid indigestion, heartburn, treatment/prevention of calcium deficiency, hyperphosphatemia in renal failure

No Official Pregnancy Category

Dosing

- Acid indigestion, heartburn:
  - Liquid:
    - 5–10 ml every 2 hours (see product-specific dosing)
    - Maximum of 8000 mg calcium carbonate/24 hours; do not use for more than 2 weeks
  - Tablets/chewable tablets:
    - 1–2 tablets every 2 hours (see product-specific dosing)
    - Maximum of 8000 mg calcium carbonate/24 hours do not use for more than 2 weeks
- Treatment/prevention of calcium deficiency: 1–2 g of elemental calcium daily in 2 to 3 divided doses with meals (variable based on serum calcium and clinical condition)

Adverse Reactions: Most Common

Constipation, bloating, gas, nausea, vomiting, abdominal pain, xerostomia

Adverse Reactions: Rare/Severe/Important

Hypercalcemia, hypophosphatemia, milk-alkali syndrome

Major Drug Interactions

Calcium Carbonate's Effect on Other Drugs

Calcium carbonate antacid preparations have been reported to decrease the pharmacologic effect/exposure of many drugs when concomitantly administered. Monitor for therapeutic efficacy and failure. Good evidence supports a significant interaction with iron salts, tetracyclines, fluoroquinolones, ketoconazole, itraconazole, rilpivirine, and thyroid hormones.

Counseling Points

- Separate administration of antacid medications by at least 2 hours from other medications
- Chew tablets completely before swallowing; do not swallow whole
- For self-medication, antacids should not be taken for > 2 weeks. Contact a physician if symptoms are not relieved promptly or symptoms return often.

Key Points

- Because of easy OTC access to these agents, it is important to assess patients for potential drug interactions and more serious symptoms that require a physician's care
- Symptoms that recur and persist beyond 2 weeks may be a sign of a more serious disease; these patients should be referred to a physician
- Calcium-containing antacids may be safely used during pregnancy; however, special consideration should be taken to ensure that the addition of calcium to other daily vitamins does not exceed the upper limit of 2,500 mg of calcium per day

ANTICHOLINERGIC/ANTISPASMODIC AGENTS

Introduction

Anticholinergic agents, such as dicyclomine, are used in the treatment of GI motility disorders, such as irritable bowel syndrome (IBS) and urinary incontinence. The use of anti-cholinergic agents is generally limited by their side effects, including dizziness, drowsiness, blurry vision, and dry mouth. Dicyclomine and oxybutynin are two of the most common agents in this class, likely because they have fewer anticholinergic effects and act mostly as antispasmodic agents. Limited data support the efficacy of these agents, and many patients are unable to tolerate therapeutic doses; therefore, they are not considered first-line therapy for IBS or urinary incontinence.

Mechanism of Action for the Drug Class

Anticholinergic agents block the action of acetylcholine at parasympathetic sites in smooth muscle, secretory glands, and the CNS

Members of the Drug Class

In this section: Dicyclomine

Others: GI anticholinergics: Hyoscyamine, scopolamine, belladonna, propantheline, atropine; urinary anticholinergics/antispasmodics: oxybutynin, tolterodine, trospium, solifenacin, darifenacin

◉ Dicyclomine

Brand Name
Bentyl

Generic Name
Dicyclomine

Rx Only

Dosage Forms
Capsule, tablet, oral solution, injectable solution

Usage
Irritable bowel syndrome, urinary incontinence, infant colic, acute enterocolitis

Pregnancy Category B

Dosing
- Oral: 20–40 mg 4 times a day
- IM: 10–20 mg 4 times a day; maximum of 1 to 2 days
- IV: Do not administer IV

Adverse Reactions: Most Common
Dry mouth, dizziness, drowsiness, blurred vision, nausea, constipation, weakness, nervousness, light-headedness (parenteral administration), local irritation (parenteral administration)

Adverse Reactions: Rare/Severe/Important
Decreased sweating, tachyarrhythmia, psychosis, difficulty breathing

Major Drug Interactions
Dicyclomine's Effect on Other Drugs
- Anticholinergic drugs: Belladonna/belladonna alkaloids may have additive anticholinergic effects/toxicities
- Acetylcholinesterase inhibitors: Theoretical interaction because they would likely antagonize the therapeutic effect of each other

Contraindications
Obstructive diseases of the GI tract, severe ulcerative colitis, reflux esophagitis, unstable cardiovascular status in acute hemorrhage, obstructive uropathy, narrow-angle glaucoma, myasthenia gravis, infants < 6 months of age

Counseling Points
- This drug may impair mental alertness; use caution when driving or engaging in tasks that require alertness
- Dicyclomine may cause constipation; increasing exercise, fluids, fruit, or fiber may help if patients experience this side effect

Key Point
Dicyclomine is not considered a first-line therapy for urinary incontinence or IBS due to a lack of data supporting its efficacy over alternative agents and high incidence of side effects. Notable side effects are dizziness, drowsiness, dry mouth, blurry vision, nausea, and nervousness.

ANTIDIARRHEAL/ANTISECRETORY AGENTS

Introduction
Bismuth subsalicylate possesses antisecretory, anti-inflammatory, antibacterial effects. Available over the counter, it is commonly used to self-treat a variety of indications, including indigestion, upset stomach, and diarrhea. Bismuth subsalicylate may also be used in combination with antibacterial and acid suppressive therapy to treat *Helicobacter pylori*. It is important to remember that an active component of this agent is salicylate, an aspirin derivative that may lead to toxicities in excessive doses or an inappropriate patient population.

Mechanism of Action for the Drug Class
The exact mechanism of action has not been determined. The salicylate moiety provides an antisecretory effect, and bismuth moiety exhibits antimicrobial activity directly against bacterial and viral GI pathogens. Bismuth also has some antacid properties.

Members of the Drug Class
In this section: Bismuth subsalicylate/bismuth subgallate
Others: None

◉ Bismuth Subsalicylate/Bismuth Subgallate

Brand Names
Pepto-Bismol, Kaopectate, Bismatrol, Devrom

Generic Names
Bismuth subsalicylate, bismuth subgallate

OTC

Dosage Forms

Oral suspension, tablet, chewable tablet

Usage

Indigestion, diarrhea, upset stomach, abdominal cramps, prevention and treatment of traveler's diarrhea, treatment of *H. pylori*–associated gastritis/ulcer (in combination only); self-medication in children and adults for the reduction of flatulence or stool odor from a colostomy or ileostomy, fecal incontinence, irritable bowel syndrome, or bariatric surgery (bismuth subgallate only)

Pregnancy Category C/D

Dosing

- Diarrhea:
  - 524–1050 mg every 30 to 60 minutes as needed (see product-specific dosing)
  - Maximum of 4 to 8 doses (4,200 mg) every 24 hours
- *H. pylori*: 524 mg 4 times a day (in combination)
- Fecal odor control (subgallate only): 1 capsule or tablet orally 4 times daily.

Adverse Reactions: Most Common

Constipation, diarrhea, nausea, grayish-black tongue discoloration, grayish-black vomiting, grayish-black discoloration of stool

Adverse Reactions: Rare/Severe/Important

Persistent tinnitus, hearing loss, nausea, vomiting, neurotoxicity with excessive doses (confusion, slurred speech, severe headache, muscle weakness, seizure)

Major Drug Interactions

Bismuth Subsalicylate/Bismuth Subgallate's Effect on Other Drugs

- Tetracycline, doxycycline: Decrease absorption and effectiveness
- Aspirin/anticoagulants: Use of multiple salicylates may lead to toxicity and increase risk of bleeding

Contraindications

Children or teenagers with influenza or chickenpox due to the risk of Reye's syndrome, hypersensitivity to salicylates (including aspirin), coagulopathy, severe GI bleeding

Counseling Points

- Medication may temporarily darken the tongue and/or stools (nonharmful)
- Chew tablet well or shake suspension well before use
- Report any changes in hearing or ringing in your ears
- If diarrhea is accompanied by high fever, blood/mucus in the stool, or continues for > 2 days, consult a physician

Key Points

- Bismuth subsalicylate is a commonly used OTC drug for a variety of GI indications
- This medication may be harmful in large doses; neurotoxicity has been reported. Any symptoms of encephalopathy should be reported to a physician.
- Bismuth subsalicylate should be avoided in children and teenagers with viral symptoms or chickenpox
- Bismuth subgallate should not be used for the treatment of diarrhea

ANTIDIARRHEALS

Introduction

Antidiarrheals are widely available over the counter and are commonly used in the symptomatic treatment of diarrhea, including symptoms of mild or uncomplicated cases of travelers' diarrhea. Concurrent fluid and electrolyte replacement is often necessary in all age groups, depending on the severity of diarrhea. Importantly, patients with bacterial enteritis should not use these agents; similarly, they should not be used if diarrhea is accompanied by high fever or blood in the stool.

Mechanism of Action for the Drug Class

Antidiarrheals act peripherally on intestinal opioid receptors, inhibiting peristalsis and prolonging transit time, reducing fecal volume, increasing viscosity, and diminishing fluid and electrolyte losses. They demonstrate antisecretory activity.

Members of the Drug Class

In this section: Loperamide
Others: Bismuth subsalicylate (see section on antidiarrheal/antisecretory agents), diphenoxylate/atropine

◉ Loperamide

Brand Name

Imodium A-D

Generic Name

Loperamide

OTC

Dosage Forms
Capsule, caplet, tablet, oral liquid

Usage
Symptomatic relief and control of acute nonspecific diarrhea (including traveler's diarrhea), treatment of chronic diarrhea associated with inflammatory bowel disease, antineoplastic agents, bowel resection

Pregnancy Category C

Dosing
- Acute diarrhea: 4 mg orally, followed by 2 mg after each loose stool, up to 16 mg/day
- Chronic diarrhea: 4 mg orally, followed by 2 mg after each loose stool until symptoms are controlled; dosage should then be slowly titrated down to the minimum dose required to control symptoms (average dose 4–8 mg/day in divided doses)
- Self-medication: 4 mg orally, followed by 2 mg after each loose stool, up to 8 mg/day

Adverse Reactions: Most Common
Abdominal pain, constipation, dizziness, drowsiness, dry mouth

Adverse Reactions: Rare/Severe/Important
Toxic megacolon, ileus, necrotizing enterocolitis

Major Drug Interactions
Loperamide's Effect on Other Drugs

CNS depressants, phenothiazines, and tricyclic antidepressants: Potentiates adverse effects

Counseling Points
- May cause drowsiness or dizziness; exercise caution while driving or performing hazardous tasks
- Consult physician if acute diarrhea lasts > 48 hours or is accompanied by blood, severe abdominal pain, distention, or fever
- Maintain adequate hydration during treatment

Key Points
- Do not use in acute diarrhea associated with bacterial enteritis or *Clostridium difficile* or for diarrhea associated with high fever or bloody stool
- Loperamide is not recommended for use in cases of acute flares of ulcerative colitis because it may increase the risk of developing toxic megacolon
- Use with caution in treatment of AIDS patients. Stop therapy at the sign of abdominal distention; cases of toxic megacolon have occurred in AIDS patients with infectious colitis.

ANTIEMETICS: PHENOTHIAZINES, TYPICAL ANTIPSYCHOTICS

Introduction
Phenothiazines are among the most commonly prescribed antiemetic agents available. They come in a wide variety of preparations for oral, rectal, and IV/IM administration, and are generally less expensive than newer antiemetics on the market. They are particularly effective for treatment of drug-induced nausea. Adverse effects, such as extrapyramidal reactions, tardive dyskinesia, orthostatic hypotension, and drug-induced Parkinson's syndrome are relatively common and are more likely to develop in elderly patients and young children. This class of drugs is also approved to treat psychiatric conditions, such as schizophrenia and anxiety; however, the drugs are no longer recommended as first-line therapy for these conditions due to their questionable efficacy and potential for significant adverse events.

Mechanism of Action for the Drug Class
These drugs have an antiemetic effect through central inhibition of dopamine receptors in the medullary chemoreceptor trigger zone. The antipsychotic effect stems from the ability of phenothiazines to block postsynaptic mesolimbic dopaminergic (D_1 and D_2) receptors in the brain.

Members of the Drug Class
In this section: Prochlorperazine
Others: Chlorpromazine, perphenazine, promethazine

◉ Prochlorperazine

Brand Names
Compazine, Compro

Generic Name
Prochlorperazine

Rx Only

Dosage Forms
Tablet, suppository, injection solution

Usage
Nausea/vomiting (including chemotherapy-induced nausea and vomiting and postoperative nausea and vomiting), schizophrenia, anxiety, psychosis/agitation related to Alzheimer's dementia (not recommended for this use), migraines and associated nausea and vomiting

Pregnancy Category C

Dosing

- Antiemetic:
  - Oral (immediate release):
    - 5–10 mg 3 to 4 times a day
    - Maximum: 40 mg daily
  - Rectal: 25 mg twice daily
  - IV/IM (deep):
    - 2.5–10 mg every 3 to 4 hours
    - Maximum: 10 mg/dose, 40 mg/day
- Postoperative:
  - IV: 5–10 mg 15 to 30 minutes before anesthesia induction—don't exceed injection/infusion rate of 5 mg/minute; may repeat once
  - IM: 5–10 mg 1 to 2 hours before anesthesia induction; may repeat once
- Hepatic dosage adjustment: Guidelines not provided by the manufacturer; however, prochlorperazine is primarily eliminated hepatically. Caution is advised because drug accumulation may occur.

Adverse Reactions: Most Common

Hypotension (IV administration), constipation, dry mouth, dizziness, extrapyramidal reactions (akathisia, dystonia, Parkinsonian symptoms)

Adverse Reactions: Rare/Serious/Important

Agranulocytosis, leukopenia, thrombocytopenia, ineffective thermoregulation, neuroleptic malignant syndrome, cholestatic jaundice, seizure (lower seizure threshold), tardive dyskinesia (long-term use), QT prolongation (mostly associated with other agents in this class)

Major Drug Interactions

Prochlorperazine's Effect on Other Drugs

- Dofetilide: Increases serum concentration
- Antagonistic action against dopaminergic agents used to treat Parkinson's disease
- CNS depressants/sedatives: Enhances CNS depression

Contraindications

Children < 2 years or < 9 kg, pediatric surgery, presence of large amounts of CNS depressants

Counseling Points

- This drug may impair mental alertness; use caution when driving or engaging in tasks that require alertness
- Notify your physician if feelings of restlessness or involuntary/spastic muscle movements occur or if you experience fever, muscle rigidity, or altered mental status

Key Points

- Prochlorperazine should not be given SUB-Q because of local irritation. If giving IV, do not administer as a bolus; give as a slow IV push (max rate of 5 mg/min) or infusion. Hypotension may occur with IV administration.
- Prochlorperazine is most commonly used for the acute treatment of generalized nausea and vomiting and nausea and vomiting related to chemotherapy. It is particularly effective for postoperative nausea and vomiting and drug- or toxin-induced nausea and vomiting.
- Although the class of phenothiazines has been associated with a significant number of adverse effects, many of these effects are seen at high doses, with chronic therapy, and in combination with other psychiatric agents. As an antiemetic, especially with short-term, as-needed use, prochlorperazine is generally well tolerated.
- Prochlorperazine has fallen out of favor as an antipsychotic agent and is rarely used for this purpose any longer

ANTIEMETICS, PHOSPHORATED CARBOHYDRATE SOLUTION

Introduction

Phosphorated carbohydrate solution is a mixture of fructose, dextrose, and phosphoric acid. It has been available over the counter for many years; however, clinical data supporting its efficacy are lacking. Importantly, this solution is the only antiemetic available over the counter with the exception of medications used for motion sickness. If phosphorated carbohydrate solution is being used to treat nausea *not* related to motion sickness, medical advice may be warranted because nausea can be a sign of a more serious underlying condition.

Mechanism of Action for the Drug Class

The combination of the hyperosmolar solution and phosphoric acid is hypothesized to act locally on the GI tract, decreasing smooth muscle contractions and delaying gastric emptying time

Members of the Drug Class

In this section: Phosphorated carbohydrate solution
Others: None

◉ Phosphoric Acid/Dextrose/Fructose

Brand Names
Emetrol, Formula EM, Nausetrol

Generic Name
Phosphoric acid/dextrose/fructose

OTC

Dosage Form
Liquid

Usage
Treatment of nausea associated with upset stomach that occurs with intestinal or stomach flu and food indiscretions

No Official Pregnancy Category

Dosing
15–30 ml; repeat dose every 15 minutes until symptoms subside (do not take for > 1 hour or > 5 doses)

Adverse Reactions: Most Common
Abdominal pain, diarrhea

Contraindication
Hereditary fructose intolerance

Counseling Points
- Do not dilute solution
- May chill in refrigerator to improve palatability
- Do not consume other liquids for 15 minutes after taking each dose

Key Points
- It is important to remember that nausea, unless related to motion sickness, may be symptom of a more serious underlying condition. If nausea does not resolve, the patient should seek medical attention from a physician.
- Phosphorated carbohydrate solution has been used off-label for motion sickness and morning sickness; however, it is recommended that all pregnant women speak with a physician before self-medicating
- This product contains a significant amount of sugar; thus, it is not recommended for use in diabetics

ANTIFLATULENTS

Introduction
Simethicone has been used as an adjunct in the treatment of various clinical conditions in which gas retention may be a problem, including postoperative gaseous distention, air swallowing, dyspepsia, infant colic, peptic ulcer, spastic or irritable colon, and diverticulitis

Mechanism of Action for the Drug Class
Decreases the surface tension of gas bubbles, thereby dispersing and preventing gas pockets in the GI system

Members of the Drug Class
In this section: Simethicone
Others: None

◉ Simethicone

Brand Names
Gas-X, Mylanta Gas, Mylicon, Phazyme

Generic Name
Simethicone

OTC

Dosage Forms
Capsule, chewable tablet, oral suspension (drops), oral disintegrating strip

Usage
Relief of bloating, pressure, and discomfort of gas; adjunctively in upper abdominal ultrasound to enhance delineation by reducing gas shadowing

Pregnancy Category
Not rated; as simethicone is not absorbed systemically following oral administration, will not cross placenta and reach fetus

Dosing
40–125 mg orally 4 times daily after meals and at bedtime as needed

Adverse Reactions: Most Common
None

Counseling Points
- This medication works best when taken after meals and at bedtime
- Avoid drinking carbonated beverages or eating foods that may cause an increase in stomach gas

Key Points

- Simethicone is a frequently used OTC medication for people of various ages, ranging from infants to adults. It may be used as needed for gas pain and discomfort.
- It works optimally when taken after meals
- Simethicone is not absorbed by the GI tract; it does not have well-documented side effects, contraindications, or drug interactions

CHLORIDE CHANNEL ACTIVATORS

Introduction

Lubiprostone is a single agent in a new class of drugs used to treat chronic idiopathic constipation and irritable bowel syndrome with constipation (IBS-C) in women. It has a novel mechanism of action, affecting chloride channels in the intestine responsible for regulating fluid balance, without any clinically significant changes in serum electrolyte concentrations. Because the vast majority of patients enrolled in the IBS-C studies were women, lubiprostone has not been approved to use for IBS-C in men due to a lack of clinical data.

Mechanism of Action for the Drug Class

Activates ClC-2 chloride channels in the intestine, promoting a chloride-rich fluid secretion into the intestine, thereby improving motility and passage of stools

Members of the Drug Class

In this section: Lubiprostone
Others: None

◉ Lubiprostone

Brand Name

Amitiza

Generic Name

Lubiprostone

Rx Only

Dosage Form

Capsule

Usage

Treatment of chronic idiopathic constipation, IBS-C in women, opioid-induced constipation in chronic noncancer pain

Pregnancy Category C

Dosing

- Chronic idiopathic constipation: 24 µg twice a day (dose may be decreased to once a day if poorly tolerated due to nausea)
- IBS-C: 8 µg twice a day
- Opioid-induced constipation: 24 µg twice a day
- Hepatic dosage adjustment:
  - Moderate hepatic impairment (Child-Pugh class B):
    - Chronic idiopathic constipation and opioid-induced constipation: 16 µg twice daily; may increase to 24 µg twice daily if tolerated and an adequate response has not been obtained with lower dosage
    - IBS-C in women: No dosage adjustment required
  - Severe hepatic impairment (Child-Pugh class C):
    - Chronic idiopathic constipation and opioid-induced constipation: 8 µg twice daily; may increase to 16–24 µg twice daily if tolerated and an adequate response has not been obtained with lower dosage
    - IBS-C: 8 µg once daily; may increase to 8 µg twice daily if tolerated and an adequate response has not been obtained at a lower dosage

Adverse Reactions: Most Common

Nausea, diarrhea, headache, dizziness, abdominal pain and distention, flatulence, vomiting, dyspepsia

Adverse Reactions: Rare/Severe/Important

Dyspnea, which may also be described as chest tightness or discomfort. Usually occurs within 30 to 60 minutes after the first dose and resolves after several hours; may occur again after subsequent doses. Not an allergic reaction. Therapy can be continued if tolerated; however, it may lead to therapy discontinuation in some patients.

Contraindications

Known or suspected mechanical GI obstruction

Counseling Points

- This medication may be taken with meals to decrease nausea
- Swallow whole, do not break or chew
- Dyspnea, also referred to as chest discomfort, may occur following the first dose. This is not an allergic reaction and generally resolves within 3 hours but may recur with subsequent doses.
- Notify your doctor if experiencing severe nausea, severe diarrhea, or dyspnea

Key Points

- Lubiprostone is considered an adjunctive therapy to diet and lifestyle modifications for the treatment of IBS-C. It is only approved for the treatment of IBS-C in females > 18 years. This is due to the fact that > 90% of clinical trial participants were women and there were insufficient data to determine the safety and efficacy in men.
- The most common side effect is nausea, particularly with the 24 µg dose. Patients may try taking the dose with food to decrease nausea. In addition, the dose may be decreased to a once-daily regimen if nausea persists.
- Dyspnea, occurring within 30 to 60 minutes following the first dose of lubiprostone, was reported in up to 3% of patients. Resolution was common after 3 hours; however, some patients may need to discontinue therapy due to intolerance.

GUANYLATE CYCLASE-C AGONISTS

Introduction

Linaclotide is one of two agents in a new class of drugs used to treat chronic idiopathic constipation (CIC) and/or irritable bowel syndrome with constipation (IBS-C).

Mechanism of Action for the Drug Class

Linaclotide and its active metabolite bind and agonize guanylate cyclase-C on the luminal surface of the intestinal epithelium. The drug increases secretion of chloride and bicarbonate into the intestinal lumen, which increases intestinal fluid and accelerates transit of fecal material. Movement of chloride and bicarbonate is modulated by cyclic guanosine monophosphate (cGMP); increases in cGMP may also relieve associated pain.

Members of the Drug Class

In this section: Linaclotide
Others: Plecanatide

◉ Linaclotide

Brand Name

Linzess

Generic Name

Linaclotide

Rx Only

Dosage Form

Capsule

Usage

Irritable bowel syndrome with constipation, chronic idiopathic constipation

Pregnancy Category C

Dosing

Irritable bowel syndrome with constipation: 290 µg once daily; chronic idiopathic constipation: 145 µg once daily; may lower to 72 µg daily based on tolerability

Adverse Reactions: Most Common

Diarrhea, abdominal pain, flatulence, abdominal distension, headache

Adverse Reactions: Rare/Severe/Important

Viral gastroenteritis, defecation urgency, fecal incontinence

Major Drug Interactions

Drugs Affecting Linaclotide

None

Linaclotide's Effect on Other Drugs

None

Contraindications

- **Black Box Warning:**
  - Contraindicated in children aged up to 6 years; avoid use in children aged 6 to 17 years.
- Contraindicated in patients hypersensitive to drug or its components and in those with proven or suspected mechanical GI obstruction.

Counseling Points

- Take drug on an empty stomach at least 30 minutes before first meal of the day
- Give dose as a whole capsule; don't break or crush capsules. Capsules may be opened and administered orally in either applesauce or with water or administered with water via a nasogastric or gastrostomy tube. If placing in applesauce, place one teaspoonful of room-temperature applesauce into a clean container. Open the capsule and sprinkle the entire contents (beads) on applesauce. Consume the entire contents immediately; do not chew the beads. Do not store the bead-applesauce mixture for later use. If placing in water, pour approximately 30 ml of room-temperature bottled water into a clean cup and open the capsule. Sprinkle the entire contents (beads) into the water, gently swirling beads and water for at least 20 seconds. Swallow the entire mixture of beads and water immediately. Add another 30 ml of water to any beads remaining in cup, swirl for 20 seconds, and swallow immediately. Do not store the bead-water mixture for later use. If giving via NG or gastrostomy tube, open the capsule, and empty the beads into a clean container with 30 ml of room temperature bottled water. Mix by gently swirling beads for at least 20 seconds Draw up the beads and water mixture into an appropriately sized catheter-tipped syringe and apply rapid and steady pressure (10 ml/10 seconds) to dispense the syringe contents into the tube. Add another 30 ml of water to any beads remaining in the container and repeat the process. After administering the bead-water mixture, flush nasogastric/ gastrostomy tube with a minimum of 10 ml of water. It is not necessary to flush all the beads through to deliver the complete dose.
- Store in original container with desiccant. Store in dry place away from moisture.

Key Points

- Monitor patient for diarrhea. Withhold or discontinue drug if diarrhea is severe. Diarrhea is most frequent within first 2 weeks of treatment but can occur at any time
- Monitor patient for blood in stools
- Risk of diarrhea and loose stools increases when drug is given with high-fat meals
- Patient should learn to identify signs and symptoms of dehydration (dizziness, confusion, loss of balance) and how to prevent dehydration
- Advise patient to stop drug and contact prescriber if severe diarrhea; severe abdominal pain; or black, tarry, or bloody stools occur

H_2 RECEPTOR ANTAGONISTS

Introduction

H_2 receptor antagonists are used for the treatment of GI disorders in which acid suppression is desired or for prevention of ulcers in critically ill patients. These agents are available as prescription products, and several agents are also available in over-the-counter doses, making access to them widespread. They are commonly used for mild gastroesophageal reflux disease (GERD); however, they have been shown to be less effective than other acid-suppressive therapies in moderate to severe disease. In the treatment of peptic ulcer disease, H_2 receptor blockers are effectively used to heal ulcers and maintain ulcer healing; however, their efficacy in NSAID-induced gastric ulcers is variable and, therefore, not usually recommended. These agents are generally very safe and well-tolerated, with an adverse-event profile similar to placebo in many studies.

Mechanism of Action for the Drug Class

Competitive inhibition of histamine at H_2 receptors of the gastric parietal cells, which ultimately reduce gastric acid secretion

Members of the Drug Class

In this section: Cimetidine, famotidine, ranitidine
Others: Nizatidine

◉ Cimetidine

Brand Name
Tagamet HB

Generic Name
Cimetidine

Rx and OTC

Dosage Forms
Injectable solution, tablet, oral solution

Usage
Treatment of GERD, prevention or relief of heartburn, acid indigestion, or sour stomach; prevention of upper GI bleeding in critically ill patients; short-term treatment and maintenance therapy of active duodenal ulcers; short-term

treatment of gastric ulcers and gastric hypersecretory states; part of a multidrug regimen for *H. pylori* eradication

Pregnancy Category B

Dosing

- Oral:
  - Rx: 300–800 mg 1 to 4 times daily (dose- and frequency-dependent on indication)
  - OTC: 200 mg twice daily
- IM/IV: 300 mg every 6 to 8 hours; infusion: 37.5 mg/hour
- Renal dosage adjustment:
  - CrCl 10–50 ml/min: Administer 50% of normal dose
  - CrCl < 10 ml/min: Administer 25% of normal dose
- Hepatic dosage adjustment: dosing adjustment in severe liver disease may be required; however, no specific recommendations are available

Adverse Reactions: Most Common

Diarrhea, dizziness, headache, somnolence, gynecomastia

Adverse Reactions: Rare/Severe/Important

Agranulocytosis, thrombocytopenia, altered mental status/confusion, necrotizing enterocolitis in fetus/newborn, cardiac arrhythmias, and hypotension (following rapid IV administration)

Major Drug Interactions

Cimetidine's Effect on Other Drugs

- Dofetilide, lidocaine, amiodarone, procainamide, quinidine, calcium channel blockers (except amlodipine, clevidipine, nicardipine), warfarin, theophylline, tricyclic antidepressants, SSRIs, phenytoin, carbamazepine, cyclosporine, sulfonylureas: Increases effect/toxicity
- Iron salts, itraconazole, ketoconazole, posaconazole, atazanavir, rilpivirine, cefditoren, dasatinib, erlotinib, clopidogrel: Decreases effect/absorption

Counseling Points

- If using cimetidine to prevent heartburn, take oral formulations 30 to 60 minutes prior to meals
- If used for self-medication, do not use if you have difficulty swallowing, are vomiting blood, or have bloody or black stools; seek medical attention
- If used for self-medication, consult a physician for heartburn or stomach pain that continues or worsens or if use is required for > 14 days

Key Points

- Cimetidine is an effective and inexpensive option for the treatment of multiple GI disorders requiring acid suppression. However, of the H_2 antagonists available, it has the most significant inhibition of multiple CYP enzymes, and; therefore, the most drug interactions; it is also associated with the highest incidence of adverse CNS effects.
- Patients with renal and severe liver dysfunction should receive an adjusted dose to prevent adverse effects, such as confusion; this is particularly true for elderly patients
- Rapid IV administration has been associated with cardiac arrhythmias and hypotension; therefore, intermittent or continuous infusions are preferred when IV administration is necessary

Famotidine

Brand Names

Pepcid, Pepcid AC, Pepcid Complete (combination famotidine/calcium carbonate/magnesium hydroxide)

Generic Name

Famotidine

Rx and OTC

Dosage Forms

Oral suspension, tablet, chewable tablet, injectable solution

Usage

Treatment of GERD, relief of heartburn and acid indigestion, stress ulcer prophylaxis in critically ill patients, maintenance therapy and treatment of duodenal ulcer, acute treatment of gastric ulcer, pathologic hypersecretory conditions, part of a multidrug regimen for *H. pylori* eradication, symptomatic relief in gastritis

Pregnancy Category B

Dosing

- Oral:
  - Rx: 20–40 mg daily or twice daily (dose and frequency depends on indication; higher doses up to 160 mg every 6 hours have been used for hypersecretory conditions)
  - OTC: 10–20 mg daily or twice daily
- IV: 20–40 mg daily or twice daily (dose- and frequency-dependent on indication; higher doses up to 160 mg every 6 hours have been used for hypersecretory conditions)
- Renal dosage adjustment: If CrCl < 50 ml/min, then administer 50% of normal dose or increase dosing interval to every 36 to 48 hours

Adverse Reactions: Most Common

Constipation, diarrhea, dizziness, headache

Adverse Reactions: Rare/Severe/Important

Thrombocytopenia, altered mental status/confusion, necrotizing enterocolitis in fetus/newborn

Major Drug Interactions

Famotidine's Effect on Other Drugs

Decreased effect/absorption of iron salts, itraconazole, ketoconazole, posaconazole, atazanavir, rilpivirine, cefditoren, erlotinib, dasatinib, delavirdine, mesalamine (sustained release)

Counseling Points

- If using to prevent heartburn, take oral formulations 10 to 60 minutes prior to meals
- Do not use for self-medication if you have difficulty swallowing, are vomiting blood, or have bloody or black stools; seek medical attention
- If used for self-medication, consult a physician for heartburn or stomach pain that continues or worsens or if use is required for > 14 days

Key Points

- Famotidine is an effective option for the treatment of multiple GI disorders requiring acid suppression and is commonly used for stress ulcer prophylaxis in the ICU setting. It is very well tolerated and has a mild adverse-event profile.
- Unlike cimetidine, famotidine is not an inhibitor of the CYP enzyme system; therefore, drug interactions are limited to those drugs with decreased absorption in the altered gastric pH
- Patients with renal dysfunction should receive dosing adjustments to prevent adverse effects, such as confusion; this is particularly true for elderly patients

◉ Ranitidine

Brand Name

Zantac

Generic Name

Ranitidine

Rx and OTC

Dosage Forms

Effervescent tablet, injectable solution, oral syrup, tablet, capsule

Usage

Treatment of GERD, relief of heartburn, indigestion, short-term and maintenance therapy of duodenal and gastric ulcers, erosive esophagitis, pathologic hypersecretory conditions, part of a multidrug regimen for *H. pylori* eradication, prevention of stress-induced ulcers in critically ill patients

Pregnancy Category B

Dosing

- Oral:
  - Rx: 150 mg one to 4 times daily (frequency-dependent on indication) or 300 mg daily (depending on indication)
  - OTC: 75 mg twice daily
- IV/IM: 50 mg every 6 to 8 hours; continuous infusion: 6.25 mg/hour; alternatively, give at 1 mg/kg/hr for hypersecretory conditions, such as Zollinger-Ellison syndrome
- Renal dosage adjustment:
  - Oral: If CrCl < 50 ml/min, then 150 mg every 24 hours
  - IM/IV: If CrCl < 50 ml/min, then 50 mg every 18 to 24 hours
- Hepatic dosage adjustment: Minor changes in half-life, distribution, clearance, and bioavailability are possible; however, dosage adjustments are not necessary

Adverse Reactions: Most Common

Abdominal pain, diarrhea, constipation, headache, fatigue

Adverse Reactions: Rare/Severe/Important

Anemia, thrombocytopenia, altered mental status/confusion, necrotizing enterocolitis in fetus or newborn, pancreatitis

Major Drug Interactions

Ranitidine's Effect on Other Drugs

- Procainamide (at doses > 300 mg): Increases effect/toxicity
- Iron salts, atazanavir, dasatinib, delavirdine, erlotinib, gefitinib, cefditoren, itraconazole, ketoconazole, posaconazole, mesalamine (sustained release): Decreases effect/absorption

Counseling Points

- If using to prevent heartburn, take 30 to 60 minutes before having foods/drinks that cause heartburn
- Do not use for self-medication if you have difficulty swallowing, are vomiting blood, or have bloody or black stools; seek medical attention
- If used for self-medication, consult a physician for heartburn or stomach pain that continues or worsens or if use is required for > 14 days
- Ranitidine effervescent granules should not be chewed, swallowed whole, or dissolved on tongue. Dissolve in at least 1 teaspoon of water; swallow when completely dissolved.

Key Points

- Because ranitidine is a weak inhibitor of CYP1A2 and CYP2D6, it has the potential to cause drug interactions, although to much less extent than cimetidine
- Ranitidine is generally very well tolerated and an effective treatment option for mild GERD symptoms and heartburn relief, especially in the outpatient setting
- Patients with renal dysfunction should receive dosage adjustments to prevent adverse effects, such as confusion; this is particularly true for elderly patients

INTEGRIN RECEPTOR ANTAGONISTS

Introduction

This group of agents are used for the treatment of refractory inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis. Integrins are proteins that have been identified as significant contributors to chronic inflammation, and integrin receptor antagonists work to slow the inflammatory response.

Mechanism of Action for the Drug Class

Vedolizumab is a humanized monoclonal antibody that binds to certain integrins, thereby decreasing inflammatory and other responses like those seen in Crohn's disease or ulcerative colitis.

Members of the Drug Class

In this section: Vedolizumab
Others: None

◉ Vedolizumab

Brand Name

Entyvio

Generic Name

Vedolizumab

Rx Only

Dosage Form

Lyophilized powder

Usage

Treatment of moderately to severely active Crohn's disease or ulcerative colitis in patients who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor-alpha (TNF-alpha) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids

Pregnancy Category B

Dosing

300 mg infused intravenously over approximately 30 minutes at 0, 2, and 6 weeks, then every 8 weeks thereafter. Must reconstitute drug with sterile water for injection and further dilute in 250 ml of sterile 0.9% sodium chloride injection prior to infusion. Infuse final product over 30 minutes. Following infusion, flush with 30 ml of 0.9% sodium chloride injection. Observe patients during infusion (until complete) and monitor for hypersensitivity reactions; discontinue if a reaction occurs.

Adverse Reactions: Most Common

Nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, extremity pain

Adverse Reactions: Rare/Severe/Important

Infusion-related reactions and hypersensitivity reactions, infections, progressive multifocal leukoencephalopathy (PML), liver injury

Major Drug Interactions

Drugs Affecting Vedolizumab

Anti-TNF agents, denosumab, pimecrolimus, tacrolimus: enhanced toxic effects and immunosuppression of vedolizumab

Vedolizumab's Effects on Other Drugs

BCG, belimumab, natalizumab, live vaccines: enhanced toxic effects of these agents.

Contraindications

None

Essential Monitoring Parameters

Screening for tuberculosis should be considered; monitor for elevations of transaminases (ALT, AST) and/or bilirubin; monitor for signs/symptoms of infection

Counseling Points

- Alert prescriber if signs of infection develop
- Notify prescriber if signs of liver injury occur such as fatigue, anorexia, right upper abdominal discomfort, or dark urine

Key Points

- Monitor patients and withhold drug for any new onset or worsening of neurologic signs and symptoms, including progressive weakness on one side of the body, limb clumsiness, visual disturbances, and alterations in thinking, memory, and orientation leading to confusion and personality changes, as these symptoms may be a sign of progressive multifocal leukoencephalopathy (PML), a rare and often fatal opportunistic infection of the central nervous system caused by the John Cunningham (JC) virus
- Discontinue use with jaundice or signs/symptoms of hepatic injury such as fatigue, anorexia, right upper abdominal discomfort, or dark urine
- Drug is not recommended in patients with uncontrolled, active, severe infections; if a serious infection develops, consider discontinuing therapy
- Use with caution in patients with a history of recurring severe infections
- Live vaccines should not be given concurrently unless the benefits outweigh the risks

LAXATIVES, BOWEL PREPARATION/BOWEL EVACUANTS

Introduction

Several agents and combinations of agents are commonly prescribed to evacuate the bowel in preparation for a colonoscopy. Although some products are available over the counter, the newest agents are available by prescription only. In order to clearly view the colon during the colonoscopy, all solid waste must be evacuated; therefore, it is extremely important that patients understand the directions for completing a bowel preparation regimen. The newer agents, discussed in this section, require less volume than the traditional 4 liter polyethylene glycol 3350 preparation product known as GoLYTELY; lower-volume preparations are generally preferred by patients. Of note, sodium phosphate preparation products have been associated with acute phosphate nephropathy, a condition resulting from phosphate crystal deposits in the renal tubules, possibly leading to permanent kidney damage.

Mechanism of Action for the Drug Class

Mechanism dependent on product

Members of the Drug Class

In this section: Polyethylene glycol 3350 (MoviPrep)
Others: Polyethylene glycol 3350 (GoLYTELY), sodium phosphate

◉ Polyethylene Glycol 3350

Brand Name

MoviPrep

Generic Name

Polyethylene glycol 3350

Rx Only

Dosage Form

Powder for oral solution

Usage

Bowel evacuation/bowel preparation for colonoscopy

Pregnancy Category C

Dosing

- MoviPrep: Administer 2 l total with an additional 1 l of clear fluid prior to colonoscopy as follows:
  - Split dose: The evening before the colonoscopy, consume 240 ml (8 oz.) every 15 minutes until 1 l is consumed, then drink 480 ml (16 oz.) of clear liquid. On the morning of the colonoscopy, repeat process with second liter given as 240 ml (8 oz.) every 15 minutes over 1 hour and then drink 480 ml (16 oz.) of clear liquid at least 2 hours before the procedure.
  - Full dose: The evening before the colonoscopy (~ 6 PM), consume 240 ml (8 oz) every 15 minutes until 1 l is consumed; 90 minutes later (~ 7:30 PM), repeat dose. Then drink 32 oz of clear liquid.

Adverse Reactions: Most Common

Abdominal pain and distension, nausea, vomiting, anal irritation, malaise, rigors, thirst, dizziness, headache, dyspepsia

Adverse Reactions: Rare/Severe/Important

Aspiration, upper GI bleed from Mallory-Weiss tear, electrolyte imbalance, ischemic colitis

Major Drug Interactions

Oral medications administered within 1 hour of the start of administration of this product may be flushed from the GI tract and not absorbed

Contraindications

Bowel obstruction, ileus, gastric retention, bowel perforation, toxic megacolon

Counseling Points

- Each powder pouch must be diluted in water before ingestion
- Oral medications may not be absorbed properly if taken within 1 hour of starting prep
- MoviPrep will make you have watery stools. Stay hydrated before, during, and after the use of MoviPrep. No solid food should be consumed from the start of the prep until after the colonoscopy.
- The first bowel movement may occur approximately 1 hour after starting the prep. Abdominal bloating and discomfort is common; if pain is severe, stop drinking MoviPrep temporarily or drink each portion over a longer time interval until symptoms diminish. If severe symptoms persist, contact your healthcare provider.

Key Points

- MoviPrep is a newer, lower-volume polyethylene glycol 3350 bowel preparation agent. It is equally effective and may cause fewer GI side effects compared with the older polyethylene glycol 3350 agent, GoLYTELY. MoviPrep does not contain sodium phosphate and has not been associated with acute phosphate nephropathy.
- Patients will experience diarrhea and the stool should have a watery consistency; this is necessary to clean the colon for optimal visualization during the colonoscopy. Blood in the stool is not expected; the patient should be advised to contact a healthcare provider if this occurs.
- Encourage patients to remain hydrated because extreme fluid loss can lead to dehydration, electrolyte imbalances, seizures, and renal dysfunction

LAXATIVES, BULK-FORMING

Introduction

Bulk-forming laxatives are fiber derivatives used in addition to dietary modifications for the treatment and prevention of constipation; they are often considered first-line therapy for treatment of simple constipation. They can also be used to increase the bulk of stool in patients with chronic, watery diarrhea. Bulk-forming laxatives usually have an effect within 12 to 24 hours and reach a maximum effect after several days. This class of medications includes several fiber products, including methylcellulose, polycarbophil, and psyllium; most agents are available over the counter.

Mechanism of Action for the Drug Class

Bulk-forming laxatives dissolve or swell in water to form an emollient gel or viscous solution that promotes peristalsis and reduces transit time

Members of the Drug Class

In this section: Psyllium
Others: Methylcellulose, polycarbophil, wheat dextrin

⦿ Psyllium

Brand Names

Fiberall, Genfiber, Konsyl, Metamucil, Reguloid

Generic Name

Psyllium

OTC

Dosage Forms

Capsule, powder, packets, wafer

Usage

Dietary fiber supplement, treatment of occasional and chronic constipation, irritable bowel syndrome, inflammatory bowel disease, diverticular disease, adjunctive agent for cholesterol lowering

No Official Pregnancy Category

Dosing

- Daily fiber recommended intake for adults 19 to 50 years:
  - Male: 38 g per day
  - Female: 25 g per day
- Up to 30 g orally daily given in divided doses of 2.5–7.5 g per dose

Adverse Reactions: Most Common

Abdominal pain and cramping, constipation, diarrhea, flatulence

Adverse Reactions: Rare/Severe/Important

Bronchospasm (following inhalation of powder), bowel obstruction/impaction, esophageal obstruction

Major Drug Interactions

Psyllium may affect how other drugs are absorbed from the GI tract; separate medications from psyllium by 1 to 2 hours

Contraindications

Intestinal obstruction, fecal impaction

Counseling Points

- Powder or packets: Mix in large glass of water or juice (≥ 8 oz.) and drink immediately. Maintain adequate hydration and fiber intake during therapy. Do not inhale powder.
- Capsules and wafers: Take each dose with ≥ 8 oz. of water
- Separate this medication from other medications by at least 1 to 2 hours
- Results may begin in 12 hours; full results may take 2 to 3 days
- Report persistent constipation; watery diarrhea; difficulty, pain, or choking with swallowing; do not use for > 1 week without consulting a physician

Key Points

- For most patients, treatment of constipation should consist of bulk-forming agents in addition to dietary modifications to increase fiber intake. Considering that most agents in this class are extremely well tolerated, they can likely be continued for daily use if directed by a physician.
- Bulk-forming laxatives must be taken with plenty of fluids (8 oz per dose) to prevent bowel/esophageal obstruction and fecal impaction; elderly patients not receiving enough fluids may be at particularly high risk for these adverse effects
- Bulk-forming laxatives are the common first-line choice to treat constipation in pregnant women if dietary changes are ineffective
- Due to the potential adsorption of concomitantly administered medications, separate administration by at least 1 to 2 hours
- Specific formulations (sugar-free, sodium-free) are available for particular patient populations with dietary restrictions

LAXATIVES, OSMOTIC/HYPEROSMOLAR

Introduction

Osmotic laxatives are commonly recommended to treat occasional constipation. Because they are hyperosmolar, these agents draw water into the bowel, softening the stool and facilitating movement through the GI tract. Polyethylene glycol 3350, discussed in this chapter, is one of the most commonly used osmotic laxatives. It is used in small doses for relief of constipation and in large doses for GI procedures to evacuate the bowel. Polyethylene glycol 3350 is particularly well known because it is available over the counter and has a benign side-effect profile. Unlike many of the other agents in this class, it generally does not cause cramping, bloating, urgency, or flatulence. Lactulose is used for difficult-to-treat constipation and is used for the treatment of hepatic encephalopathy in the setting of cirrhosis.

Mechanism of Action for the Drug Class

Polyethylene glycol is a hyperosmolar agent that causes retention of water in the stool, resulting in a softer stool and more frequent bowel movements. Lactulose helps to produce osmosis and distension in the colon; this distension promotes peristalsis and movement of stool.

Members of the Drug Class

In this section: Polyethylene glycol 3350 (MiraLAX), lactulose
Others: Glycerin, sorbitol

◉ Polyethylene Glycol 3350

Brand Name

MiraLAX

Generic Name

Polyethylene glycol 3350

OTC

Dosage Form

Powder for oral solution

Usage

Constipation (occasional and chronic)

Pregnancy Category

Use in pregnancy should be avoided unless other medications are contraindicated due to lack of information

Dosing

17 g of powder (1 capful filled to line) dissolved in 4–8 oz. of water daily; speak to a physician regarding use > 7 days

Adverse Reactions: Most Common

Nausea, abdominal fullness, diarrhea, flatulence, stomach cramps

Adverse Reactions: Rare/Severe/Important

Dermatitis, rash, urticaria

Major Drug Interactions

None reported

Contraindications

Bowel obstruction, known or suspected

Counseling Points

- Mix 17 g of powder (1 capful filled to line) in 4–8 oz. of water and drink immediately. May take 2 to 4 days to produce a bowel movement.
- Maintain adequate fluid intake throughout use
- If used as self-medication, do not use this medicine for > 1 week unless directed by your healthcare provider
- Consult your healthcare provider if you have nausea, vomiting, abdominal pain, renal dysfunction, diarrhea, or blood in stools. Discontinue use if severe pain, cramping, or nausea persists.

Key Points

- Prolonged, frequent, or excessive use could lead to dehydration and electrolyte imbalance
- MiraLAX may be better tolerated than other laxatives with regard to adverse GI effects (i.e., gas, cramping, bloating); however, it can take up to 2 to 4 days to see results
- MiraLAX has been shown to be safe and effective for up to 6 months in trials treating chronic constipation; however, patients should consult their physician prior to use beyond 1 week

◉ Lactulose

Brand Names

Constulose, Enulose, Generlac, Kristalose

Generic Name

Lactulose

Rx Only

Dosage Forms

Oral solution, packets

Usage

Constipation, portal-systemic encephalopathy

Pregnancy Category B

Dosing

10–20 g (15–30 ml or 1 to 2 packets) daily; may increase to 40 g (60 ml or 2 to 4 packets) daily, if necessary

Adverse Reactions: Most Common

Nausea, vomiting, abdominal discomfort, diarrhea, flatulence, belching, stomach cramps

Adverse Reactions: Rare/Severe/Important

Dehydration, hypokalemia, hyponatremia

Major Drug Interactions

None reported

Contraindications

Bowel obstruction, known or suspected; patients who require a low-galactose diet.

Counseling Points

- Mix oral solution with fruit juice, water, or milk; if using packets, dissolve packet contents in 120 ml (4 oz.) of water.
- Maintain adequate fluid intake throughout use
- Consult your healthcare provider if you have nausea, vomiting, abdominal pain, renal dysfunction, diarrhea, or blood in stools. Discontinue use if severe pain, cramping, diarrhea, or nausea persists.

Key Points

- Prolonged, frequent, or excessive use could lead to dehydration and electrolyte imbalance
- Geriatric, debilitated patients who receive lactulose for more than 6 months should have serum electrolytes checked periodically

LAXATIVES, STOOL SOFTENERS

Introduction

Stool softeners are a preferred type of laxative in patients who have conditions in which straining at defecation should be avoided, such as recent myocardial infarction, recent rectal surgery, painful hemorrhoids, and hernias. Docusate sodium is used to treat constipation associated with hard, dry stools and is considered safe to use in geriatric patients and pregnant women. Because the main effect of docusate sodium is stool softening, not stimulation, it is better at preventing constipation than treating it; to treat constipation, docusate may be combined with a stimulant laxative.

Mechanism of Action for the Drug Class

Stool softeners reduce surface tension at the oil–water interface of the feces, allowing water and lipids to penetrate the stool, resulting in stool softening

Members of the Drug Class

In this section: Docusate sodium
Others: None

◉ Docusate Sodium

Brand Names

Colace, Correctol Extra Gentle, Doc-Q-Lace,

Generic Name

Docusate sodium

OTC

Dosage Forms

Capsule, oral solution, tablet

Usage

Constipation; promotes easy passage of stool in patients who should avoid straining; constipation with dry, hard stool

Pregnancy Category

No reports linking the use of docusate sodium with congenital defects have been located

Dosing

50–360 mg daily divided into 2 to 3 doses (usual dose is 100 mg 1 to 2 times per day)

Adverse Reactions: Most Common

Abdominal pain and cramping

Major Drug Interactions

No known significant interactions

Contraindication

Intestinal obstruction

Counseling Points

- Maintain adequate hydration
- Do not chew or break capsules; swallow whole
- Report persistent constipation

Key Points

- Docusate sodium works by hydrating the stool to facilitate easy passage through the intestinal tract in patients with dry, hard bowel movements. It is probably more effective at preventing constipation in patients who should avoid straining rather than treating acute episodes.
- For opiate-induced constipation, docusate sodium should be combined with a stimulant agent

LAXATIVES, STIMULANT

Introduction

For patients with acute constipation, stimulant laxatives are generally considered safe and effective for short-term intermittent use. If laxative treatment is required for > 1 week, the patient should consult a physician to determine whether there is an underlying condition that requires additional treatment. Because the stimulant agents may commonly cause defecation urgency, abdominal cramping, and fluid and electrolyte imbalances, they are not recommended as first-line agents in geriatric patients or those requiring therapy for chronic constipation. Commonly, these agents are used to effectively treat and prevent opiate-induced constipation. At one time, it was thought that chronic use of these agents could lead to physical dependence; however, currently, there are no data to support this theory; the main concern with chronic use is generally the risk of fluid and electrolyte imbalance.

Mechanism of Action for the Drug Class

Directly stimulates the smooth muscle of the intestine at the colonic nerve plexus, causing peristalsis; may also alter intestinal water and electrolyte secretion

Members of the Drug Class

In this section: Bisacodyl, senna
Others: None

◉ Bisacodyl

Brand Names

Bisco-Lax, Correctol, Dulcolax, Fleet Bisacodyl

Generic Name

Bisacodyl

OTC

Dosage Forms

Tablet, suppository, enema

Usage

Constipation, bowel evacuation/bowel preparation for colonoscopy

No Official Pregnancy Category

Dosing

- Oral: 5–15 mg as a single dose (up to 30 mg may be given for complete bowel evacuation)
- Rectal: 10 mg as a single dose

Adverse Reactions: Most Common

Abdominal pain and cramps, nausea, vomiting, rectal burning

Adverse Reactions: Rare/Severe/Important

Electrolyte and fluid imbalance

Major Drug Interaction

Antacids may diminish the therapeutic effect of bisacodyl by causing early dissolution of the tablet

Contraindication

Bowel obstruction

Counseling Points

- Usually produces a bowel movement in 6 to 12 hours when taken orally; 15 to 60 minutes when given rectally
- Not for chronic use, consult a physician if constipation persists or if symptoms of nausea, pain, or abdominal distention become severe
- Maintain adequate fluid intake

Key Points

- Bisacodyl is recommended for intermittent, short-term use in acute constipation. It is also frequently prescribed as part of bowel preparation regimens prior to colonoscopy.
- Stimulant laxatives are not recommended for routine or chronic use in elderly patients due to their adverse

event profile. Agents that are preferred in this patient population include bulk-forming stool softeners and osmotic agents.

Senna

Brand Names
Senokot, Senexon, Senna-Lax, Ex-Lax

Generic Name
Senna

OTC

Dosage Forms
Tablet, oral liquid, oral disintegrating strip, chewable tablet

Usage
Constipation, bowel evacuation/bowel preparation for colonoscopy

Pregnancy Category
No human teratogenicity or fetal toxicities have been documented

Dosing
- Constipation: 15 mg once daily up to a maximum of 70–100 mg daily divided into 2 doses
- Bowel evacuation: Doses and regimens are variable; doses of up to 130 mg may be used

Adverse Reactions: Most Common
Abdominal cramping, diarrhea, nausea, vomiting

Adverse Reactions: Rare/Severe/Important
Electrolyte and fluid imbalance

Contraindications
Bowel obstruction, acute intestinal inflammation, abdominal pain of unknown origin

Counseling Points
- Usually produces a bowel movement in 6 to 12 hours
- Not for chronic use, consult a physician if constipation persists or if symptoms of nausea, pain, or abdominal distention become severe
- Maintain adequate fluid intake

Key Points
- Senna is recommended for intermittent, short-term use in acute constipation. It is also frequently prescribed as part of bowel preparation regimens prior to colonoscopy.
- Stimulant laxatives are not recommended for routine or chronic use in elderly patients due to their adverse-event profile. Agents that are preferred in this patient population include bulk-forming stool softeners and osmotic agents.

MIXED RECEPTOR AGENTS

Introduction
Drugs in this category are primarily used for irritable bowel syndrome (IBS). IBS is a condition in which crampy abdominal pain, diarrhea, and/or constipation are present. Some IBS patients exhibit predominance of either constipation or diarrhea; these agents are designed to help relieve those symptoms. Eluxadoline is the only drug in this category of mixed receptor agents.

Mechanism of Action for the Drug Class
Eluxadoline is a mixed μ-opioid receptor agonist, delta opioid receptor antagonist, and kappa opioid receptor agonist. The drug acts locally to reduce abdominal pain and diarrhea in patients suffering from irritable bowel syndrome with diarrhea (IBS-D) without constipating side effects.

Members of the Drug Class
In this section: Eluxadoline
Others: None

Eluxadoline

Brand Name
Viberzi

Generic Name
Eluxadoline

Rx Only

Controlled Substance/Schedule
c-IV

Dosage Form
Tablet

Usage
Treatment of irritable bowel syndrome with diarrhea (IBS-D)

Pregnancy Category
There are no studies with eluxadoline in pregnant women that inform of any drug-associated risks.

Dosing

Adults: 100 mg twice daily taken with food. If patients do not have a gallbladder, cannot tolerate the 100 mg dose, are receiving OATP1BI inhibitors such as cyclosporine, gemfibrozil, atazanavir, lopinavir, ritonavir, saquinavir, tipranavir, rifampin, or eltrombopag, or have mild (Child-Pugh class A) to moderate (Child-Pugh class B) impairment, give 75 mg twice daily.

Adverse Reactions: Most Common

Constipation, nausea, abdominal pain, upper respiratory infection, vomiting

Adverse Reactions: Rare/Severe/Important

Spasm of Sphincter of Oddi, pancreatitis

Major Drug Interactions

Drugs Affecting Eluxadoline

- Alosetron, anticholinergics, opioids, cyclosporine, gemfibrozil, antiretrovirals (atazanavir, lopinavir, ritonavir, saquinavir, tipranavir), rifampin, eltrombopag, ciprofloxacin, gemfibrozil, fluconazole, clarithromycin, paroxetine, and bupropion: increased exposure to eluxadoline

Eluxadoline's Effect on Other Drugs

- Alosetron, anticholinergics, opioids: increase constipative effects
- Rosuvastatin, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide,
- Quinidine, sirolimus, tacrolimus: increased concentrations of these drugs

Contraindications

Severe hepatic impairment (Child-Pugh class C), known or suspected biliary duct obstruction, or sphincter of Oddi disease or dysfunction, alcoholism, alcohol abuse, alcohol addiction, or drink more than three alcoholic beverages/day, history of pancreatitis; structural diseases of the pancreas, including known or suspected pancreatic duct obstruction, severe constipation, or sequelae from constipation, or known or suspected mechanical gastrointestinal obstruction

Essential Monitoring Parameters

Monitor patients without a gallbladder for new or worsening abdominal pain, with or without nausea and vomiting, or acute biliary pain with liver or pancreatic enzyme elevations; if any of the above occur, discontinue drug

Counseling Points

- Take medication with food
- Discontinue drug if constipation lasts more than 4 days
- Don't take alosetron or loperamide, opioids or anticholinergics on a chronic basis due to the potential for constipation

Key Points

- Drug can cause spasms and/or pancreatitis, so discontinue use if patients experience symptoms, such as acute worsening of epigastric or right upper quadrant pain that may radiate to the back/shoulder with or without nausea/vomiting or if liver function tests and/or pancreatic enzymes elevate
- As a μ-agonist, eluxadoline has some potential for drug abuse and psychological dependence, so monitor carefully

MU (μ)-RECEPTOR ANTAGONISTS

Introduction

μ-Receptors are specific targets for opioids to provide analgesia, but in many instances, these same targets can cause side effects, such as constipation once activated. μ-receptor antagonists, such as naloxone, have historically been used in the treatment of opioid overdose, but newer agents have been specifically formulated to treat the side effects resulting from chronic use of opioids for pain relief.

Mechanism of Action for the Drug Class

Naloxegol is a μ-opioid receptor antagonist similar to naloxone; in fact, it is composed of naloxone combined with a polyethylene glycol polymer. This combination limits the drug's ability to cross the blood-brain barrier. When administered at usual doses, naloxegol functions in tissues, such as the GI tract, and decreases the constipation associated with chronic opioid use.

Members of the Drug Class

In this section: Naloxegol
Others: None

◉ Naloxegol

Brand Name

Movantik

Generic Name
Naloxegol

Rx Only

Dosage Form
Tablet

Usage
Treatment of opioid-induced constipation in adult patients with chronic noncancer pain

Pregnancy Category C

Dosing
Opioid-induced constipation: 25 mg once daily in the morning on an empty stomach; if unable to tolerate initial dosage or if must use with concurrent moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, verapamil): reduce dose to 12.5 mg once daily. If CrCl < 60 ml/min and in end-stage renal disease, give 12.5 mg once daily initially but if tolerated and opioid-induced constipation symptoms continue, may increase to 25 mg once daily with careful monitoring for increased adverse effects.

Administration Point
For patients unable to swallow tablet whole, may crush the tablet into a powder and mix with 120 ml of water and drink immediately; refill glass with 120 ml water, stir, and drink. If giving via NG feeding tube: Flush tube with 30 ml water using a 60 ml syringe. Crush tablet into a powder and mix with approximately 60 ml of water; draw up the mixture using the 60 ml syringe and administer through the NG tube. Rinse the same container used to prepare the dose with approximately 60 ml of water; draw up the water using the same syringe and use all of the water to flush the NG tube and any remaining medicine.

Adverse Reactions: Most Common
Abdominal pain, diarrhea, nausea, flatulence, vomiting, headache

Adverse Reactions: Rare/Severe/Important
Opioid withdrawal

Major Drug Interactions
Drugs Affecting Naloxegol

CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, diltiazem, erythromycin, verapamil, grapefruit, or grapefruit juice): increased naloxegol concentrations; CYP3A4 inducers (rifampin, carbamazepine, St. John's Wort): decreased naloxegol concentrations

Naloxegol's Effect on Other Drugs

Other opioid antagonists—increased risk of withdrawal

Contraindications
Known or suspected GI obstruction or at increased risk of recurrent obstruction; concomitant use with strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole)

Essential Monitoring Parameters
None

Counseling Points
- Administer on an empty stomach at least 1 hour prior to or 2 hours after the first meal of the day
- Swallow tablets whole; do not chew

Key Points
- Monitor for symptoms of opioid withdrawal
- Severe abdominal pain and/or diarrhea can occur at any time but especially during the first few days of therapy; pain may range from crampy pain to GI perforation
- Discontinue drug if severe symptoms occur

PROKINETIC AGENTS

Introduction
Metoclopramide is classified as both an antiemetic and prokinetic agent. It is frequently used in the treatment of gastroparesis and chemotherapy-induced nausea and vomiting. Although metoclopramide is generally well tolerated, recent data have led to an FDA black box warning regarding chronic metoclopramide use and an increased risk of developing tardive dyskinesia.

Mechanism of Action for the Drug Class
Metoclopramide has a dual mechanism of action. It blocks dopamine receptors in the chemoreceptor zone in the CNS and also enhances the response of acetylcholine in the upper GI tract, causing enhanced motility and accelerating gastric emptying.

Members of the Drug Class

In this section: Metoclopramide
Others: None

◉ Metoclopramide

Brand Names

Reglan, Metozolv ODT

Generic Name

Metoclopramide

Rx Only

Dosage Forms

Injectable solution, tablet, syrup, orally disintegrating tablet (ODT)

Usage

Diabetic gastroparesis, prevention/treatment of nausea and vomiting associated with chemotherapy, generalized nausea and vomiting, gastroesophageal reflux disease (GERD), postpyloric placement of enteral feeding tubes

Pregnancy Category B

Dosing

- GERD, gastroparesis: 10–15 mg PO/IV/IM 4 times daily, given 30 minutes before meals and at bedtime
- Chemotherapy-induced nausea/vomiting:
  - IV: 1–2 mg/kg 30 minutes before chemotherapy, and repeated every 2 hours for 2 doses, then every 3 hours for 3 doses
  - Alternate dosing for low-risk chemotherapy: 10–40 mg PO/IV every 4 to 6 hours
- Renal dosage adjustment: If CrCl ≤ 40 ml/min, then administer 50% of the normal dose

Adverse Reactions: Most Common

Drowsiness, fatigue, restlessness, insomnia, headache, dizziness, nausea, extrapyramidal reactions (generally in the form of dystonic reactions or Parkinson-like symptoms)

Adverse Reactions: Rare/Severe/Important

Depression, neuroleptic malignant syndrome (NMS), tardive dyskinesia (long-term use)

Major Drug Interactions

Drugs Affecting Metoclopramide

Succinylcholine, anticholinergics: Antagonize effects; Droperidol: Enhance adverse/toxic effects

Metoclopramide's Effect on Other Drugs

- Anti-Parkinson's agents: Diminishes therapeutic effect secondary to opposite mechanisms of action
- Antipsychotic agents: Increases risk of EPS, tardive dyskinesia
- CNS depressants: Potentiates sedative effects
- Serotoninergic antidepressants: Increases risk of serotonin syndrome

Contraindications

GI obstruction, perforation, or hemorrhage; pheochromocytoma; history of seizures or concomitant use of other agents likely to increase extrapyramidal reactions

Counseling Points

- Do not remove ODT from packaging until time of administration. Do not use if tablet is broken or crushed. Using dry hands, place tablet on tongue and allow to dissolve. Swallow with saliva.
- If used for gastroparesis, take 30 minutes prior to meals
- Notify your physician if you experience any spastic or involuntary movements, altered mental status, or palpitations
- Drowsiness and dizziness may occur. Use caution while driving or performing tasks that require alertness.

Key Points

- Use of metoclopramide remains widespread despite well-known side effects; this is likely because options to treat gastroparesis are limited and metoclopramide is recommended as a first-line therapy. The most common side effects are drowsiness, restlessness, and insomnia. Rare but serious side effects include EPS, NMS, and the risk of serotonin syndrome with concomitant agents that affect serotonin. Depression, ranging from mild to severe, has also occurred in patients without a previous history of depression.
- Dystonic reactions are more common in elderly patients and young children/adults. They occur more frequently with higher doses.
- In 2009, the FDA issued a Black Box Warning for the risk of tardive dyskinesia with high doses and prolonged use of metoclopramide

PROTON PUMP INHIBITORS

Introduction

Proton pump inhibitors (PPIs) are well tolerated and a relatively safe option for the treatment of GI disorders requiring acid-suppression therapy. They are considered first-line therapy in the treatment of moderate to severe GERD symptoms, erosive esophagitis, and treatment of NSAID-induced ulcers in the setting of continued NSAID use. A PPI-based multidrug regimen is also the first-line treatment for eradication of *H. pylori*–associated ulcers because PPIs have been shown to be more effective than H_2 antagonist–based regimens. With such widespread use in recent years, data have emerged linking the use of these agents to an increased risk of pneumonia, *C. difficile* infection, osteoporosis-related bone fractures, and hypomagnesemia.

Mechanism of Action for the Drug Class

PPIs must be activated within the gastric parietal cell. Once activated, they bind to the H^+/K^+-ATPase, inactivate the acid pump, and stop the secretion of hydrochloric acid into the stomach.

Usage for the Drug Class

Acute treatment and maintenance therapy for erosive esophagitis; treatment of GERD; part of a multidrug regimen for H. pylori eradication; prevention of gastric ulcers associated with continuous NSAID therapy; long-term treatment of pathologic hypersecretory conditions, including Zollinger-Ellison syndrome; stress ulcer prophylaxis in critically ill patients; relief of heartburn and indigestion

Adverse Reactions for the Drug Class: Most Common

Headache, dizziness, somnolence, diarrhea, constipation, nausea

Adverse Reactions for the Drug Class: Rare/Severe/Important

- Associated with the following (causality currently under investigation): *C. difficile*–associated diarrhea, community-acquired pneumonia, and hospital-acquired pneumonia
- Long-term use (> 1 year): Possible risk of osteoporosis-related bone fracture, hypomagnesemia, and vitamin B_{12} deficiency

Major Drug Interactions for the Drug Class

Drugs Affecting Proton Pump Inhibitors

Rifampin, St. John's wort: Decrease efficacy/concentration of omeprazole

Proton Pump Inhibitors' Effects on Other Drugs

- Itraconazole, ketoconazole, posaconazole, atazanavir, nelfinavir, cefditoren, dasatinib, erlotinib, mesalamine derivatives, mycophenolate mofetil, pazopanib, rilpivirine, velpatasvir: Decrease efficacy/absorption
- Tacrolimus (except pantoprazole), citalopram, possibly escitalopram, cilostazol, phenytoin: Increase efficacy/concentration
- Clopidogrel: Omeprazole may decrease efficacy

Counseling Points for the Drug Class

- Take 1 hour before meal, usually recommended to take before breakfast
- Do not crush or chew tablets
- Do not use for self-medication if you have difficulty swallowing, are vomiting blood, or have bloody or black stools; seek medical attention
- If used for self-medication, consult a physician if heartburn or stomach pain continues or worsens or if use is required for > 14 days

Key Points for the Drug Class

- For short-term use, PPIs are very well tolerated with few serious side effects. For this reason, they are often overprescribed by physicians and overused by patients. It may take up to 72 hours to achieve optimal effectiveness and symptom improvement.
- Overuse of these agents has led to concern regarding the potential for adverse effects, such as increased risk of pneumonia, *C. difficile* infection, bone fractures, and hypomagnesemia. These adverse effects have not been evaluated in a prospective study and are currently under review. Limit use to the lowest effective dose for the shortest duration.
- PPIs are generally considered interchangeable; selection of agent is usually based on cost and formulary considerations. IV formulations are generally more expensive than oral and not more efficacious; if a patient is able to take medications by mouth, oral therapy usually is preferred.
- Multiple PPIs are available over the counter; thus, healthcare providers should assess patients for prolonged use, potential drug interactions, or symptoms of more serious disease that require a physician's attention

Members of the Drug Class

In this section: Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole

Others: Dexlansoprazole, omeprazole/sodium bicarbonate (combination agent)

◉ Esomeprazole

Brand Name

Nexium

Generic Name

Esomeprazole

Rx Only

Dosage Forms
Capsules, oral granules for suspension, injectable solution

Pregnancy Category B

Dosing
- Oral/IV: 20–40 mg 1 to 2 times daily (dose- and frequency-dependent on indication)
- IV infusion: 80 mg bolus, followed by 8 mg/hour for 72 hours; convert to oral form thereafter
- Hepatic dosage adjustment: In cases of severe hepatic impairment (Child-Pugh Class C), maximum dose is 20 mg per day

Administration Points
- If using granules, empty the 2.5 or 5 mg packet into a container with 5 ml (1 teaspoon) of water or empty the 10-, 20-, or 40-mg packet into a container with 15 ml (1 tablespoon) of water and stir; leave 2 to 3 minutes to thicken. Stir and drink within 30 minutes.
- The esomeprazole capsule can be opened and contents mixed with 1 tablespoon of applesauce. Swallow immediately; mixture should not be chewed or warmed.

Lansoprazole
Brand Name
Prevacid

Generic Name
Lansoprazole

Rx and OTC

Dosage Forms
Capsule, orally disintegrating tablet (ODT), suspension

Pregnancy Category B

Dosing
- Oral:
  - Rx: 15–30 mg 1 to 3 times daily (dose- and frequency-dependent on indication)
  - OTC: 15 mg daily for 14 days; treatment may be repeated after 4 months

Administration Points
- Do not swallow ODTs whole and do not chew. Place tablet on tongue and allow to dissolve (with or without water) until particles can be swallowed.
- Lansoprazole capsules may be opened and the intact granules sprinkled on 1 tablespoon of applesauce, Ensure pudding, cottage cheese, yogurt, or strained pears. The granules should then be swallowed immediately. They may also be opened and emptied into about 60 ml orange juice, apple juice, or tomato juice; mix and swallow immediately.

Omeprazole
Brand Name
Prilosec

Generic Name
Omeprazole

Rx and OTC

Dosage Forms
Capsule, tablet, granules for suspension, powder for suspension

Pregnancy Category
No controlled studies exist; use during pregnancy only when clearly needed, no other options exist, and when benefits justify fetal risk

Dosing
- Oral:
  - Rx: 20–40 mg 1 to 2 times daily (dose- and frequency-dependent on indication)
  - OTC: 20 mg daily for 14 days; treatment may be repeated after 4 months

Administration Points
- Capsules may be opened and contents added to 1 tablespoon of applesauce, use immediately; do not chew or warm
- Granules for oral suspension: Empty the contents of the 2.5 mg packet into 5 ml of water (or 10 mg packet into 15 ml of water); stir. Note that the suspension should be left to thicken for 2 to 3 minutes prior to administration.
- Granules for oral suspension: For NG tube administration, add 5 ml of water into a catheter-tipped syringe, and then add the contents of a 2.5 mg packet (15 ml water for the 10 mg packet); shake. Note that the suspension should be left to thicken for 2 to 3 minutes prior to administration.
- Oral suspension: Reconstitute in a catheter-tipped syringe, shake well, allow 2 to 3 minutes to thicken. Administer within 30 minutes of reconstitution. Use NG tube or gastric tube that is a size 6 French or larger; flush the syringe and tube with water.

Pantoprazole
Brand Name
Protonix

Generic Name
Pantoprazole

Rx Only

Dosage Forms
Tablet, injectable solution, granules for suspension

Pregnancy Category B

Dosing

- Oral/IV push: 40–80 mg 1 to 2 times daily (dose- and frequency-dependent on indication)
- IV infusion: 80 mg bolus, followed by 8 mg/hour IV drip for 72 hours

Administration Point

The delayed-release oral suspension should only be administered in apple juice or applesauce and taken about 30 minutes before a meal; sprinkle intact granules on 1 tablespoon of applesauce and swallow within 10 minutes of preparation, or empty intact granules into 5 m1 of apple juice, stir for 5 seconds, and swallow immediately, then rinse container once or twice with apple juice and swallow. For NG administration, connect a plungerless 60 m1 catheter tip syringe to a greater than or equal to 16 French nasogastric tube; empty packet contents into barrel of syringe, add 10 ml of apple juice and tap on syringe to empty. Add additional 10 ml of apple juice to rinse and repeat with another 2–10 ml of apple juice. Empty syringe of all granules. Do not administer with any other liquid or food.

◉ Rabeprazole

Brand Name

AcipHex

Generic Name

Rabeprazole

Rx Only

Dosage Forms

Tablet, capsule sprinkle

Pregnancy Category B

Dosing

20 mg 1 to 2 times daily, up to 60 mg twice daily (dose- and frequency-dependent on indication)

Administration Point: Open capsule and sprinkle entire contents on a small amount of soft food (e.g., applesauce, fruit, or vegetable-based baby food, yogurt) or empty contents into small amounts of room temperature liquid (e.g., infant formula, apple juice, pediatric electrolyte solution). Administer whole dose within 15 minutes of preparation. Don't swallow capsule whole.

SUBSTANCE P/NEUROKININ 1/SEROTONIN-3 (5-HT$_3$) RECEPTOR ANTAGONIST

Introduction

This group of combination products combines two agents with unique qualities to treat nausea and vomiting secondary to chemotherapy. Oral palonosetron prevents nausea and vomiting during the acute phase of vomiting after cancer chemotherapy, and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.

Mechanism of Action for the Drug Class

Netupitant is a selective antagonist of human substance P/neurokinin 1 (NK1) receptors; these receptors act as a trigger for nausea and vomiting. Palonosetron is a 5-HT$_3$ receptor antagonist that acts on serotonin subtype-3 (5-HT$_3$) receptors that are present peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the brain. Palonosetron binds to 5-HT$_3$ receptors, blocking the signal to the vomiting center in the brain, thus preventing nausea and vomiting.

Members of the Drug Class

In this section: netupitant/palonosetron

Others: None

◉ Netupitant/Palonosetron

Brand Name

Akynzeo

Generic Name

Netupitant/palonosetron

Rx Only

Dosage Form

Capsule

Usage

Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy

Pregnancy Category C

Dosing

- Highly emetogenic chemotherapy (including cisplatin-based chemotherapy): One capsule (300 mg netupitant/0.5 mg palonosetron) administered approximately 1 hour prior to the start of chemotherapy with

dexamethasone 12 mg administered orally 30 minutes prior to chemotherapy on day 1 and 8 mg orally once daily on days 2 to 4.

- Chemotherapy not considered highly emetogenic (anthracyclines and cyclophosphamide-based chemotherapy): One capsule approximately 1 hour prior to the start of chemotherapy with dexamethasone 12 mg administered orally 30 minutes prior to chemotherapy on day 1; administration of dexamethasone on days 2 to 4 is not necessary.

Adverse Reactions: Most Common

Dyspepsia, fatigue, constipation, erythema, headache, asthenia

Adverse Reactions: Rare/Severe/Important

Serotonin syndrome

Major Drug Interactions

Drugs Affecting Netupitant/Palonosetron

CYP3A4 inducers (rifampin): reduced netupitant concentrations; CYP3A4 inhibitors (ketoconazole): increased netupitant concentrations; serotonergic drugs (linezolid, methylene blue, SSRIs, SNRIs, triptans): increased exposure to serotonin, possibly resulting in serotonin syndrome

Netupitant/Palonosetron's Effect on Other Drugs

CYP3A4 substrates (dexamethasone, midazolam, docetaxel, paclitaxel, etoposide, irinotecan, cyclophosphamide, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine): increased systemic effects of these agents

Contraindications

None

Essential Monitoring Parameters

Monitor AST, ALT, total bilirubin

Counseling Points

- Administer with or without food 1 hour prior to chemotherapy
- Seek immediate medical attention if any signs or symptoms of a hypersensitivity reaction occur while taking this drug or if symptoms of serotonergic syndrome occur, such as changes in mental status, autonomic instability, neuromuscular symptoms, with or without gastrointestinal symptoms

Key Points

- Avoid use in patients with severe hepatic impairment (Child-Pugh score > 9) or severe renal impairment
- Serotonin syndrome with concomitant use of this drug and other serotonergic agents (such as medications to treat depression and migraines) can occur

REVIEW QUESTIONS

1. Which of the following brand: generic name pairs do *not* match?
   a. Zofran: ondansetron
   b. Aloxi: palonosetron
   c. Mylanta: calcium carbonate
   d. Tagamet: cimetidine

2. Which of the following points concerning magnesium hydroxide/aluminum hydroxide is *false*?
   a. Patients should consult their doctors if symptoms persist for > 2 weeks
   b. Chalky taste is a common side effect
   c. Other medications should be separated by 2 hours if using antacids
   d. It is used commonly for hypophosphatemia

3. Which of the following is the correct indication for bismuth subgallate?
   a. Acid reflux
   b. Diarrhea
   c. Reduction of stool odor
   d. Nausea

4. Which of the following adverse effects is *not* associated with bismuth subsalicylate?
   a. Grayish-black stools
   b. Hair loss
   c. Neurotoxicity
   d. Nausea

5. Which of the following is *not* one of the available dosage forms of bismuth products?
   a. Injection
   b. Oral tablets
   c. Chewable tablets
   d. Suspension

6. Which of the following medications does *not* requires adjustment for hepatic insufficiency?
   a. Lubiprostone
   b. Ondansetron
   c. Esomeprazole
   d. Calcium carbonate

7. Which of the following is the mechanism of action of esomeprazole?
   a. It acts peripherally on μ-receptors
   b. It binds to H^+/K^+-ATPase and inactivates the acid pump
   c. It blocks the action of acetylcholine at parasympathetic sites
   d. It competitively inhibits histamine at H_2 receptors

8. Which of the following is a contraindication for Emetrol therapy?
   a. Acetaminophen allergy
   b. Baseline ECG changes
   c. Depression
   d. Hereditary fructose intolerance

9. Which of the following adverse effects has been associated with lubiprostone?
   a. Drug-induced Parkinson's disease
   b. Dyspnea
   c. Tardive dyskinesia
   d. All of the above

10. Which of the following drugs is available over the counter?
   a. Lubiprostone
   b. Loperamide
   c. Diphenoxylate/atropine sulfate
   d. Metoclopramide

11. Which of the following agents may be used for its antispasmodic activity?
   a. Dicyclomine
   b. Ranitidine
   c. Ondansetron
   d. Netupitant/palonosetron

12. A patient approaches the pharmacy counter to ask for advice regarding over-the-counter antacids. He has had a burning sensation in his stomach for the last 3 weeks, and the antacid he is currently using (Tums) is not working. He is asking you for another choice of antacid. What do you recommend to this patient?
   a. Aluminum hydroxide/magnesium hydroxide
   b. Mylanta
   c. Simethicone
   d. Refer him to a physician

13. Which of the following agents is a laxative?
   a. Psyllium
   b. Ranitidine
   c. Magnesium hydroxide/aluminum hydroxide
   d. Simethicone

14. Which of the following counseling statements regarding proton pump inhibitors is true?
   a. They are considered first-line in treating of moderate to severe GERD symptoms
   b. Contact a physician if using for more than 3 days
   c. Data are emerging that these drugs cause hypermagnesemia
   d. All of the above are true

15. Which of the following routes of administration is incorrect for prochlorperazine?
   a. Intravenous
   b. Intramuscular
   c. Oral
   d. Subcutaneous

16. Which of the following statements regarding ondansetron is false?
   a. It is used in chemotherapy-induced nausea and vomiting.
   b. The maximum dose given intravenously is 32 mg in a single dose.
   c. ECG changes are seen with this drug.
   d. The dose must be adjusted in patients with Child-Pugh class C liver impairment.

17. Which drug is contraindicated when given with ondansetron?
   a. Apomorphine
   b. Prochlorperazine
   c. Ranitidine
   d. Omeprazole

18. Psyllium is best described as what kind of laxative?
   a. Bulk-forming laxative
   b. Osmotic laxative
   c. Stimulant laxative
   d. Stool softener

19. Which of the following agents is used as a laxative and for portal-systemic encephalopathy?
   a. Famotidine
   b. Lactulose
   c. Pantoprazole
   d. Senna

20. Which of the following drugs is used for stress ulcer prophylaxis in critically ill patients?
   a. Calcium carbonate
   b. Famotidine
   c. Lubiprostone
   d. Linaclotide

21. Which of the following statements is true regarding eluxadoline?

- **a.** It is used for irritable bowel syndrome with diarrhea
- **b.** It is used for ulcer prophylaxis in noncritically ill patients
- **c.** Hepatitis is a major side effect
- **d.** All of the above

22. Which of the following statements regarding Akynzeo is *false*?

- **a.** The drug is prescription only
- **b.** It is a combination of a 5-HT_3 antagonist and a laxative
- **c.** It is sometimes given with dexamethasone
- **d.** Drug interactions can occur when given with CYP3A4 drugs

23. Which of the following products contain bismuth?

- **a.** Dulcolax
- **b.** Imodium
- **c.** Mylicon
- **d.** Pepto-Bismol

24. Naloxegol has been associated with all of the following adverse effects, *except*:

- **a.** Abdominal pain
- **b.** Diarrhea
- **c.** Neuroleptic malignant syndrome
- **d.** Opioid withdrawal

25. Which of the following is true regarding vedolizumab?

- **a.** It is contraindicated in elderly patients
- **b.** It is used in the treatment of Crohn's disease only
- **c.** It is considered an integrin receptor antagonist
- **d.** It should be infused over 8 hours

26. Which of the following patients should avoid linaclotide?

- **a.** A 14-year-old child
- **b.** A patient diagnosed with mechanical GI obstruction
- **c.** An infant that is 9 months old
- **d.** All of the above patients should avoid this drug

27. Dicyclomine is indicated for treating the symptoms of _____.

- **a.** Heartburn
- **b.** Constipation
- **c.** Irritable bowel syndrome
- **d.** Nausea

28. Which of the following is an appropriate dosing for oral lactulose?

- **a.** 15 mg PO every 6 hours
- **b.** 15 ml PO daily
- **c.** 240 ml PO every 6 hours
- **d.** 1000 mg PO every 12 hours

29. Metoclopramide may be used for which of the following indications?

- **a.** Bowel evacuation prior to colonoscopy
- **b.** Diabetic gastroparesis
- **c.** Inflammatory bowel disease
- **d.** Urinary incontinence

30. Which of the following agents will decrease the efficacy of omeprazole?

- **a.** Rifampin
- **b.** Clopidogrel
- **c.** Magnesium hydroxide/aluminum hydroxide suspension
- **d.** Bisacodyl

CHAPTER 9

Hematologic Agents

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ANTICOAGULANTS, COUMARIN DERIVATIVES

Introduction

Warfarin is an oral anticoagulant used to reduce the formation of pathologic clots. Its exceptional efficacy in a diverse set of disease states, oral administration, and lack of renal clearance are its benefits. These are tempered by its narrow therapeutic index and significant drug–drug, drug–diet, drug–disease interactions and need for intensive monitoring to ensure safety and efficacy. Its major adverse effect is bleeding.

Mechanism of Action for the Drug Class

Warfarin inhibits the carboxylation (activation) of the vitamin K–dependent clotting factors II, VII, IX, and X, thereby increasing the time it takes for blood to clot. Warfarin is the only anticoagulant that prevents activation of new clotting factors, and it exerts no effect against already-active clotting factors, which accounts for its slow onset and offset of action. Warfarin is an anticoagulant that stabilizes active pathologic clots so that they cannot embolize, prevents formation of new pathologic clots, and restores homeostasis so the body's fibrinolytic system can slowly dissolve active pathologic clots.

Members of the Drug Class

In this section: Warfarin
Others: None

◉ Warfarin

Brand Names

Coumadin, Jantoven

Generic Name

Warfarin

Rx Only

Dosage Forms

Tablet, injection for IV use (rarely used clinically)

Usage

Prophylaxis and treatment of deep venous thrombosis (DVT) and its extension and/or pulmonary embolism (PE); prophylaxis and treatment of stroke in high-risk patients with atrial fibrillation; prophylaxis and treatment of the thromboembolic complications associated with cardiac valve replacement reduces risk of death, recurrent myocardial infarction, and thromboembolic events, such as stroke and systemic embolization, after myocardial infarction, postoperative prophylaxis of DVT/PE in patients who have undergone hip or knee replacement surgery

Pregnancy Category X (Category D for women with mechanical heart valves)

Dosing

- Initial dose: Warfarin therapy should generally begin with the average dose requirement of 5 mg per day for the first few days, with subsequent dosing based on the INR response
- Initial dosage adjustments: Patients expected to have lower dosage requirements (i.e., malnourished, active liver disease, on interacting medications) should be initiated on 2.5 mg per day
- Maintenance dose is patient specific and initial dose is adjusted, based on weekly total dosage requirements, to achieve and maintain therapeutic INR

Pharmacokinetic Monitoring

INR goal is usually 2 to 3 for most indications, but 2.5 to 3.5 for most mechanical mitral cardiac valve replacements

Adverse Reactions: Most Common

Bleeding

Adverse Reactions: Rare/Severe/Important

Severe bleeding (Intracranial, retroperitoneal, intraocular), purple toe syndrome, skin necrosis

Major Drug Interactions

Drugs Affecting Warfarin

- Amiodarone, fluconazole, metronidazole, ciprofloxacin, erythromycin, prednisone, sulfamethoxazole/trimethoprim: Potentiate INR
- Carbamazepine, rifampin: Decrease INR
- Antiplatelet agents (Aspirin, NSAIDs, thienopyridines, SSRIs) or concomitant anticoagulants: Increased risk of bleeding

Contraindications

Hemorrhagic tendencies-active bleeding or situations where risk of bleeding outweighs potential benefit

Essential Monitoring Parameters

Prothrombin Time/INR-Monitor a minimum of monthly for efficacy, the goal is usually 2 to 3 except in mechanical mitral cardiac valves, in which it is usually 2.5 to 3.5; signs and symptoms of bleeding

Counseling Points

- Explain importance of blood test monitoring; INR testing required every 3 days to every 4 weeks
- Risk of bleeding: Monitor for blood in urine, stool, nosebleeds, hemoptysis
- Drug–drug, drug–herbal interactions: Inform your doctor when initiating or discontinuing any medication, including herbal and OTC medications
- Drug–food interaction: Keep vitamin K intake consistent and avoid large amounts of grapefruit and cranberry juice (controversial)
- Alcohol: Binge drinking will increase INR
- Avoid or take precautions (e.g., helmet, protective clothing) when participating in contact sports or activities with high risk of trauma due to bleeding risk
- Have an ID card in your wallet or a medical bracelet noting that you are taking warfarin in case of emergency
- Warfarin is pregnancy category X (D for mechanical heart valves): Discuss with your doctor before attempting to become pregnant or use appropriate contraception

Key Points

- **Black Box Warning:**
  - Warfarin has a risk of major bleeding. INR monitoring is required for all treated patients. Drugs, diet, and other changes can affect INR levels. Patients need education about bleeding prevention measures and symptoms to report.
- Warfarin offers the advantage of being an oral anticoagulant with established safety and efficacy data in a wide range of clotting disorders, and no restrictions on use in patients with renal disease. Its benefits are tempered by its need for intensive monitoring, drug-drug, drug-disease, and drug-diet interactions, which present quality-of-life concerns.
- Generally, stop 3 to 5 days before surgical procedures, may need "bridge" with injectable anticoagulant in high-risk patients to prevent clots during delayed onset and offset. Warfarin also takes at least 5 days to be fully effective.
- CHF exacerbations and hyper/hypothyroidism can significantly affect INR
- Drugs that affect INR (CYP450 interactions) can still be given concomitantly with warfarin; but the warfarin dose will need to be adjusted to keep the INR therapeutic. However, medications with antiplatelet effects may minimally affect the INR but will increase the risk of bleeding with concomitant use.
- Vitamin K (phytonadione) is the antidote

DIRECT FACTOR Xa INHIBITORS

Introduction

Rivaroxaban and apixaban are oral anticoagulants that inhibit factor Xa. They have been studied and are used for stroke prevention in atrial fibrillation, prevention of DVT/PE in patients who have undergone knee/hip replacement and for treatment of DVT/PE. They are oral anticoagulants, which are alternatives to warfarin therapy in appropriate patients. They require no therapeutic monitoring and have limited drug–diet interactions, but use is limited because they have significant drug–drug interactions, limited indications have been studied and they are cleared renally. Their major adverse effect is bleeding.

Mechanism of Action for the Drug Class

Direct factor Xa inhibitors work by selectively and reversibly inhibiting active clotting factor Xa without the use of antithrombin. These medications stabilize active pathologic clots to prevent their embolization, prevent formation of new pathologic clots and restore homeostasis so the body's fibrinolytic system can slowly dissolve active pathologic clots.

Members of the Drug Class

In this section: Rivaroxaban, Apixaban
Others: Edoxaban

Usage for the Drug Class

Postoperative prophylaxis of DVT/PE in patients who have undergone hip or knee replacement surgery, prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, prophylaxis, and treatment of DVT and PE

Key Points for the Drug Class

- **Black Box Warnings:**
  - Premature discontinuation of these agents may increase the risk of thrombosis. High-risk patients who are being transitioned to warfarin should be "bridged" with an injectable anticoagulant to avoid this risk.
  - Spinal/epidural hematoma may occur if patients undergo neuraxial anesthesia or spinal puncture while on these agents
- These medications are a convenient alternative to warfarin as they have demonstrated similar or superior efficacy but they have a predictable dose response so they do not require regular laboratory monitoring and dose adjustments (i.e., INR monitoring with warfarin) to ensure efficacy. These medications also have fewer drug–drug, drug–disease, and drug–diet interactions than warfarin.
- Currently, rivaroxaban and apixaban should ONLY be used for FDA-labeled indications until more studies are completed. Never use these medications in patients with mechanical prosthetic cardiac valves.
- For rivaroxaban: 10 mg dose may be taken with or without food but 15 mg and 20 mg dose should be taken WITH food to optimize efficacy
- Bleeding is the most common adverse effect. Drug–drug interactions and renal function must be monitored to prevent drug accumulation and increased bleeding risk.
- The chromogenic anti-Xa levels for direct Xa inhibitors is the laboratory test used to quantify drug levels, but it is currently not readily available for clinical use. This test is not generally indicated but would be useful in specific clinical situations, i.e., when a patient requires emergent surgery.
- These medications have short half-lives and adherence is essential to efficacy. Prothrombin complex concentrate (PCC) may be used to manage serious bleeding and Andexanet Alfa (AndexXa, Portola Pharmaceuticals) is awaiting approval as an antidote.

⦿ Apixaban

Brand Name

Eliquis

Generic Name

Apixaban

Rx Only

Dosage Form

Tablet

Pregnancy Category B

Dosing

- Thromboprophylaxis following knee/hip replacement: 2.5 mg PO BID
- Nonvalvular atrial fibrillation: 5 mg PO BID. In patients with two or more of the following; age ≥ 80 years, SrCr ≥ 1.5 mg/dl or body weight ≤ 60 kg, reduce dose to 2.5 mg PO BID
- DVT and PE: 10 mg PO BID x 7 days then reduce dose to 5 mg PO BID. Dose may be reduced to 2.5 mg PO BID after at least 6 months of therapy
- Note: Patients with ESRD have not been studied
- Conversion from warfarin: Discontinue warfarin and initiate apixaban when INR falls to < 2
- Conversion to warfarin: Initiate warfarin and a parenteral anticoagulant 24 hours after discontinuing apixaban
- Conversion from anticoagulants other than warfarin: Discontinue the other drug and initiate apixaban at the usual time of the next dose of the other anticoagulant
- Conversion to an anticoagulant other than warfarin: Discontinue apixaban and initiate the other anticoagulant at the time the next apixaban dose is due

Pharmacokinetic Monitoring

None required

Adverse Reactions: Most Common

Bleeding

Adverse Reactions: Rare/Severe/Important

Severe bleeding (cerebral, retroperitoneal, intraocular)

Major Drug Interactions

Drugs Affecting Apixaban

- Aspirin, NSAIDs, concomitant anticoagulants or antiplatelet agents: Increase risk of bleeding; use when benefit outweighs risk
- Clarithromycin, conivaptan, itraconazole, ketoconazole, and ritonavir: Increase drug levels and risk of bleeding—reduce dose to 50% or avoid use if already taking lower dose
- Carbamazepine, phenytoin: Reduced efficacy of apixaban

Contraindications

Active pathologic bleeding

Essential Monitoring Parameters

- Renal function: SrCr at least yearly as decreased renal function may lead to drug accumulation and bleeding
- Bleeding: Monitor signs and symptoms
- Adherence: Medication has short half-life so adherence is critical to ensure efficacy

Counseling Points

- Risk of bleeding: Monitor for blood in urine, stool, nosebleeds, hemoptysis
  - Take without regard to meals
  - Inform your doctor if you start taking any new medications, including herbal or OTC medications
- Bleeding: Monitor signs and symptoms
- Adherence: Medication has short half-life so adherence is critical to ensure efficacy

◉ Rivaroxaban

Brand Name

Xarelto

Generic Name

Rivaroxaban

Rx Only

Dosage Form

Tablet

Usage

Postoperative prophylaxis in patients who have undergone hip or knee replacement surgery, prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, treatment of DVT and PE

Pregnancy Category C

Dosing

- Thromboprophylaxis following knee/hip replacement: 10 mg PO once daily. Avoid use if CrCl < 30 ml/min.
- Nonvalvular atrial fibrillation: 20 mg PO once daily. 15 mg PO once daily if CrCl 15–50 ml/min and avoid use if CrCl < 15 ml/min. MUST TAKE WITH A MEAL.
- DVT and PE: Initial 15 mg PO twice daily for 3 weeks following acute DVT/PE, followed by 20 mg PO once daily. Use starter pack to ensure correct dosing. Avoid use if CrCl < 30 ml/min. MUST TAKE WITH A MEAL.
- Conversion from warfarin: Discontinue warfarin and initiate rivaroxaban when INR falls to < 3.0
- Conversion to warfarin: Initiate warfarin and a parenteral anticoagulant 24 hours after discontinuing rivaroxaban
- Conversion from continuous infusion unfractionated heparin: Initiate rivaroxaban at the time of heparin discontinuation
- Conversion to continuous infusion unfractionated heparin: Initiate continuous infusion unfractionated heparin 24 hours after discontinuation of rivaroxaban

Pharmacokinetic Monitoring

None required. However, measurement of prothrombin time (not the INR) may be used to detect presence of rivaroxaban if the reagent is sufficiently sensitive to rivaroxaban.

Adverse Reactions: Most Common

Bleeding (gastrointestinal)

Adverse Reactions: Rare/Severe/Important

Severe bleeding (intracerebral, retroperitoneal, intraocular)

Major Drug Interactions

Drugs Affecting Rivaroxaban

- Aspirin, NSAIDs, concomitant anticoagulants or antiplatelet agents, and selective serotonin reuptake inhibitors (SSRIs): Increase risk of bleeding; use when benefit outweighs risk cautiously
- Clarithromycin, conivaptan, itraconazole, ketoconazole, and ritonavir: Increase drug levels and risk of bleeding and should be avoided
- Carbamazepine, phenytoin, rifampin, St. John's Wort: Decrease efficacy and should be avoided

Contraindications

Active pathologic bleeding; renal failure

Essential Monitoring Parameters

- Renal function: SrCr at least yearly as decreased renal function may lead to drug accumulation and bleeding
- Bleeding: Monitor signs and symptoms
- Adherence: Medication has short half-life so adherence is critical to ensure efficacy

Counseling Points

- Risk of bleeding: Monitor for blood in urine, stool, nosebleeds, hemoptysis
- For hip or knee replacement surgery: 10 mg dose may be taken with or without food
- For atrial fibrillation and DVT/PE: 15 mg and 20 mg dose should be taken WITH food
- Inform your doctor if you start taking any new medications, including herbal or OTC medications
- Risk of bleeding: Monitor for blood in urine, stool, nosebleeds, hemoptysis
- Adherence: Medication has short half-life so adherence is critical to ensure efficacy

DIRECT THROMBIN INHIBITORS

Introduction

The direct thrombin inhibitors are anticoagulants used in various clinical situations. Bivalirudin is available IV and may be used in patients with acute coronary syndromes undergoing percutaneous coronary intervention (PCI) as well as in patients with a history of heparin-induced thrombocytopenia (HIT). Dabigatran is the first orally approved direct thrombin inhibitor, and it is more commonly used for stroke prevention in patients with nonvalvular atrial fibrillation, treatment, and prophylaxis of DVT/PE. It is an oral alternative to warfarin therapy in appropriate patients. It does not require therapeutic monitoring and has limited drug-diet interactions, but its use may be limited due to drug–drug interactions, renal clearance, limited indications studied, and risk of dyspepsia. The major side effect with the direct thrombin inhibitors is bleeding.

Mechanism of Action for the Drug Class

The direct thrombin inhibitors reversibly inhibit coagulation by preventing thrombin-mediated effects, such as cleavage of fibrinogen to fibrin monomers and thrombin-induced platelet aggregation. These medications stabilize active pathologic clots to prevent their embolization, prevent formation of new pathologic clots and restore homeostasis so the body's fibrinolytic system can slowly dissolve active pathologic clots.

Members of the Drug Class

In this section: Bivalirudin, dabigatran
Others: Argatroban, desirudin

⦿ Bivalirudin

Brand Name

Angiomax

Generic Name

Bivalirudin

Rx Only

Dosage Forms

Injection, IV

Usage

Unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI) (moderate-high risk) undergoing early invasive strategy, STEMI undergoing primary PCI, HIT

Pregnancy Category B

Dosing

- UA/NSTEMI undergoing early invasive strategy:
  - 0.1 mg/kg IV bolus, followed by 0.25 mg/kg/hour IV. Once PCI is determined to be warranted, give an additional bolus of 0.5 mg/kg IV and increase infusion rate to 1.75 mg/kg/hour IV during procedure.
  - Renal dosage adjustment:
    - CrCl 10–29 ml/min: Decrease initial infusion rate to 1 mg/kg/hour IV
    - Dialysis: Begin infusion at 0.25 mg/kg/hour IV
- STEMI undergoing PCI:
  - 0.75 mg/kg IV bolus, followed by initial infusion of 1.75 mg/kg/hour IV during procedure
  - Renal dosage adjustment:
    - CrCl 10–29 ml/min: Decrease initial infusion rate to 1 mg/kg/hour IV
    - Dialysis: Initial infusion rate of 0.25 mg/kg/hour IV
- HIT: 0.15–0.2 mg/kg/hour IV; adjust to aPTT 1.5 to 2.5 times baseline value and overlap with warfarin for at least 5 days until INR is within target range

Pharmacokinetic Monitoring

Depends on indication for use of bivalirudin (ACT or aPTT). If using aPTT, therapeutic range is different from for UFH.

Adverse Reactions: Most Common

Bleeding

Adverse Reactions: Rare/Severe/Important

Anaphylaxis, major bleeding (intracranial, retroperitoneal, intraocular)

Major Drug Interactions

Antiplatelets (i.e., Aspirin, NSAIDs) or concomitant anticoagulants: Increase risk of bleeding

Contraindication

Active bleeding

Counseling Points

- There is a risk of bleeding. Monitor for blood in urine, stool, nosebleeds, hemoptysis.
- Irritation may occur around the IV site
- Watch for signs of anaphylaxis, such as chest tightness; swelling of face, lips, tongue, or throat

Key Point

Only given IV. Bivalirudin is more frequently used in the cardiac catheterization lab while argatroban is more commonly used as treatment for heparin-induced thrombocytopenia

⦿ Dabigatran

Brand Name

Pradaxa

Generic Name

Dabigatran

Rx Only

Dosage Form

Capsule

Usage

Prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, prevention and treatment of DVT/PE, prevention of DVT/PE following hip replacement

Pregnancy Category C

Dosing

- Prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation:
  - 150 mg orally twice daily
  - Renal dosage adjustment:
    - CrCl < 30 ml/min: Dabigatran use has not been studied in clinical trials in this patient population although dosage recommendations exist
    - CrCl 15–30 ml/min: 75 mg orally twice daily
    - CrCl <15 ml/min or requiring hemodialysis: Use not recommended
- Treatment of DVT/PE: 150 mg orally twice daily. Avoid use if CrCl < 30 ml/min
- DVT prophylaxis following hip replacement surgery: 220 mg PO once daily after hemostasis is achieved
- Conversion from a parenteral anticoagulant:
  - Enoxaparin: Initiate dabigatran ≤ 2 hours prior to the time of the next scheduled dose of the parenteral anticoagulant
  - Heparin: Initiate dabigatran at the time of discontinuation if heparin given continuously
- Conversion to a parenteral anticoagulant:
  - CrCl >30 ml/min: Wait 12 hours after the last dose of dabigatran before initiating a parenteral anticoagulant
  - CrCl <30 ml/min: Wait 24 hours after the last dose of dabigatran before initiating a parenteral anticoagulant
- Conversion from warfarin: Discontinue warfarin and initiate dabigatran when INR < 2.0
- Conversion to warfarin:
  - CrCl >50 ml/min: Initiate warfarin 3 days before discontinuation of dabigatran
  - CrCl 31–50 ml/min: Initiate warfarin 2 days before discontinuation of dabigatran
  - CrCl 15–30 ml/min: Initiate warfarin 1 day before discontinuation of dabigatran
  - CrCl < 15 ml/min: Use not recommended

Pharmacokinetic Monitoring

Not routinely used, but aPTT values > 2.5 may indicate over anticoagulation

Adverse Reactions: Most Common

Bleeding, dyspepsia

Adverse Reactions: Rare/Severe/Important

Major bleeding (intracranial, retroperitoneal, intraocular), increased risk of MI (controversial)

Major Drug Interactions

- Antiplatelets (i.e., Aspirin, NSAIDs) or concomitant anticoagulants: Increase risk of bleeding
- Carbamazepine, phenytoin, rifampin, St. John's wort: Decrease efficacy and should be avoided
- Amiodarone, clarithromycin, quinidine, verapamil: Increase risk of bleeding; should be avoided in patients with CrCl 15–30 ml/min
- Dronedarone, itraconazole: Increase risk of bleeding; dose of dabigatran should be reduced in patients with CrCl 30–50 ml/min

Contraindication

Active bleeding

Essential Monitoring Parameters

- Renal function: SrCr at least yearly as decreased renal function may lead to drug accumulation and bleeding
- Bleeding: Monitor signs and symptoms
- Adherence: Medication has short half-life so adherence is critical to drug efficacy

Counseling Points

- Capsules must be swallowed whole. Do not break, chew, or open capsules.
- Keep medication in original bottle; discard 4 months after opening original container
- May be taken without regard to meals but taking with meals may decrease dyspepsia
- Drug–drug interactions: Inform your doctor when initiating or discontinuing any medication
- Risk of bleeding: Monitor for blood in urine, stool, nosebleeds, hemoptysis

Key Points

- **Black Box Warnings:**
  - Premature discontinuation of these agents may increase the risk of thrombosis. High risk patients should be "bridged" to warfarin with an injectable anticoagulant to avoid this risk.
  - Spinal/epidural hematoma may occur if patients undergoing neuraxial anesthesia or spinal puncture while on these agents
- The antidote is idarucizumab (Praxbind), a monoclonal antibody that is administered as 5G IV in 2 divided infusions
- Use of activated charcoal may be considered if ingestion occurred < 2 hours prior to presentation.
- The Ecarin Clotting Time is the laboratory test used to quantify drug levels but it is currently not readily available for clinical use. This test is not generally indicated but would be useful in specific clinical situations, i.e., when a patient requires emergent surgery. The PTT is elevated with dabigatran use but levels cannot be used to quantify the drug effect.
- Multiple drug–drug interactions for dabigatran exist

HEPARINS, UNFRACTIONATED

Introduction

Unfractionated heparin (UFH) is an injectable anticoagulant used to prevent and treat arterial and venous thromboses. UFH's use is limited by its short half-life, which requires a continuous infusion to maintain therapeutic levels and its propensity to cause the life-threatening adverse effect heparin-induced thrombocytopenia (HIT). UFH has largely been replaced by newer heparin formulations, such as low molecular weight heparins and fondaparinux. However, UFH is still the treatment of choice for patients with severe renal dysfunction or those needing invasive procedures that require temporary disruptions in anticoagulation. UFH is often used as a "bridge" to maintenance therapy with warfarin.

Mechanism of Action for the Drug Class

UFH binds to antithrombin and accelerates antithrombin's ability to inhibit active clotting factors IXa, Xa, XIa, XIIa, and IIa. UFH stabilizes active pathologic clots to prevent their embolization, prevents formation of new pathologic clots, and restores homeostasis so the body's fibrinolytic system can slowly dissolve active pathologic clots.

Members of the Drug Class

In this section: Unfractionated heparin
Others: None

◉ Unfractionated Heparin

Brand Names

Various

Generic Names

Heparin, UFH

Rx Only

Dosage Forms

Injection, IV infusion for treatment doses (SUB-Q administration has poor absorption and it is very difficult to maintain therapeutic levels with this route), SUB-Q injection can be used for DVT prophylaxis

Usage

Prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism (PE), peripheral arterial embolism, atrial fibrillation with high risk of stroke; diagnosis and treatment of acute and chronic consumption coagulopathies (disseminated intravascular coagulation); prevention of postoperative deep vein thrombosis (DVT) and PE in high-risk medical and surgical patients; prevention of clotting in arterial and heart surgery, blood transfusions, extracorporeal circulation, dialysis procedures, and blood samples; "bridge" to warfarin therapy to prevent cerebrovascular accident in patients with cardiac valve replacements or active pathologic clot

Pregnancy Category C

Dosing

- IV infusion for treatment of DVT/PE thromboembolism: 80 units/kg (range: 50–100 units/kg) IV bolus, followed by 18 units/kg per hour (range: 15–25 units/kg per hour) continuous IV infusion. Adjust dosage to target aPTT.
- Acute coronary syndrome: 60–70 units/kg IV bolus (maximum 5,000 units), followed by 12–15 units/kg per hour continuous IV infusion (maximum 1000 units/hour). Adjust dosage to target aPTT.
- Prophylaxis of DVT/PE for medical or surgical patients' postoperative thromboembolism: 5000 units SUB-Q every 8 to 12 hours

Pharmacokinetic Monitoring

- Partial thromboplastin time (PTT) or aPTT: Institution-specific values: Correlates with 0.3–0.7 antifactor Xa units. Therapeutic aPTT will change based on lab equipment and lab medium used at an institution—make sure to know your current therapeutic aPTT range for UFH.
- Activated clotting time (ACT) used in cardiac catheterization lab and for CABG when higher doses are used

Adverse Reactions: Most Common

Bleeding

Adverse Reactions: Rare/Severe/Important

HIT type I and type II, osteoporosis (with prolonged use), major bleeding (intracranial, retroperitoneal, intraocular)

Major Drug Interactions

Drugs Affecting Heparin

Anticoagulants, antiplatelets, thrombolytics: Increase bleeding risk

Contraindications

Active or history of HIT, severe thrombocytopenia; uncontrolled active bleeding except when due to disseminated intravascular coagulation (DIC); suspected intracranial hemorrhage; not for IM use; not for use when appropriate blood coagulation tests cannot be obtained at appropriate intervals (applies to full-dose heparin only)

Essential Monitoring Parameters

- aPTT (except for SQ prophylactic dose) or ACT
- CBC (platelets for HIT and hemoglobin for bleeding)

Counseling Points

- Note that there is a risk of bleeding. Monitor for blood in urine and stool and watch for nosebleeds.
- Use SQ or IV, never IM due to risk of hematoma

Key Points

- Does not cross placenta in pregnancy; however, difficult to maintain therapeutic levels with SUB-Q administration. LMWH is the drug of choice in pregnancy.
- High risk of osteoporosis with extended use
- Protamine sulfate is antidote
- Must monitor aPTT regularly for treatment dosing. Half-life is 1 hour when aPTT is therapeutic; however, half-life increases exponentially when supratherapeutic. Usually held for 4 hours before surgery if aPTT is initially therapeutic.
- Monitor platelets frequently to assess for HIT
- Never administer IM due to risk of hematoma

HEPARINS, LOW MOLECULAR WEIGHT

Introduction

Enoxaparin and dalteparin are low molecular weight heparins (LMWH) that have a similar anticoagulant effect to unfractionated heparin (UFH). The LMWHs have largely replaced UFH because of better SUB-Q absorption; a longer half-life, allowing for less-frequent dose administration and outpatient use; and a much lower risk of HIT and osteoporosis. The major adverse effect is bleeding.

Mechanism of Action for the Drug Class

LMWH binds to antithrombin and accelerates antithrombin's ability to inhibit active clotting factors Xa and IIa. Its MOA is similar to UFH but its anti-factor Xa activity is greater than anti-factor IIa activity. LMWHs stabilize active pathologic clots to prevent their embolization, prevent formation of new pathologic clots, and restore homeostasis so the body's fibrinolytic system can slowly dissolve active pathologic clots.

Usage for the Drug Class

Prophylaxis and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE); unstable angina/non-Q-wave myocardial infarction. Used concomitantly as a "bridge" to chronic warfarin use

Members of the Drug Class

In this section: Dalteparin, enoxaparin
Others: None

◉ Dalteparin

Brand Name

Fragmin

Generic Name

Dalteparin

Rx Only

Dosage Form

Injection (SUB-Q)

Usage

Prophylaxis and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE); unstable angina/non-Q-wave myocardial infarction

Pregnancy Category B

Dosing

- DVT/PE prophylaxis:
  - Hip replacement surgery (three dosing strategies exist):
    - Postoperative: 2500 units SUB-Q 4 to 8 hours after surgery followed by 5000 units SUB-Q once daily for maintenance therapy
    - Preoperative (starting day of surgery): 2500 units SUB-Q within 2 hours before surgery followed by 2500 units SUB-Q 4 to 8 hours after surgery and 5000 units SUB-Q once daily thereafter for maintenance therapy
    - Preoperative (starting evening prior to surgery): 5000 units SUB-Q 10 to 14 hours before surgery. Administer 5000 units SUB-Q 4 to 8 hours after surgery followed by 5000 units SUB-Q once daily thereafter for maintenance therapy.
  - Abdominal surgery:
    - Low risk: 2500 units SUB-Q 1 to 2 hours prior to surgery then once daily
    - High risk: 5000 units SUB-Q the evening prior to surgery and then once daily
- DVT/PE treatment:
  - 200 units/kg SUB-Q once daily (FDA approved in cancer patients and can decrease dose to 150 IU/Kg SQ daily for months 2 to 6) or
  - 100 units/kg SUB-Q twice daily
  - Initiate concomitant warfarin therapy when appropriate and continue dalteparin for a minimum of 5 days and until a therapeutic anticoagulant effect has been achieved (INR: 2.0–3.0)
- Unstable angina/non-Q-wave MI: 120 units/kg SUB-Q (maximum dose: 10000 units) every 12 hours in conjunction with oral aspirin therapy
- Avoid use or monitor anti-Xa levels (rarely done in clinical practice) if CrCl < 30 ml/min

Pharmacokinetic Monitoring

Generally, no monitoring is required. However, anti-Xa levels may be indicated to monitor if used in patients with obesity or severe renal dysfunction and in pregnancy and pediatric populations. Monitoring also may be used in patients with abnormal coagulation parameters or with bleeding. Goal dalteparin peak anti-Xa levels (drawn 4 to 6 hours after patient has received 3 to 4 doses) are usually 0.5–1.5 units/ml for once-daily dosing.

◉ Enoxaparin

Brand Name

Lovenox

Generic Name

Enoxaparin

Rx Only

Dosage Form

Injection (SUB-Q), can be given IV for acute coronary syndrome

Usage

Prophylaxis and treatment of DVT and PE; unstable angina/non-Q-wave myocardial infarction

Pregnancy Category B

Dosing

- DVT/PE prophylaxis:
  - Hip or knee replacement surgery:
    - 30 mg every 12 hours SUB-Q with initial dose given within 12 to 24 hours postoperatively for 7 to 10 days
    - Renal dosage adjustment: 30 mg SUB-Q every 24 hours for renal insufficiency (estimated CrCl 10–30 ml/min)
  - Abdominal or high-risk surgery: 40 mg once-daily SUB-Q with initial dose given 2 hours prior to surgery for 7 to 10 days
  - Medically ill/immobility: 40 mg SUB-Q once-daily continued for up to 14 days
- DVT/PE treatment:
  - Outpatient DVT treatment: 1 mg/kg SUB-Q every 12 hours
  - Inpatient: DVT with or without PE:
    - 1 mg/kg SUB-Q every 12 hours *or*
    - 1.5 mg/kg SUB-Q once daily
  - Renal dosage adjustment: 1 mg/kg SUB-Q every 24 hours for renal insufficiency (CrCl 10–30 ml/min) —not well studied
  - Initiate concomitant warfarin therapy when appropriate and continue enoxaparin for a minimum of 5 days and until a therapeutic anticoagulant effect has been achieved (INR: 2.0–3.0)
- Unstable angina/non-Q-wave MI:
  - 1 mg/kg SUB-Q every 12 hours in conjunction with oral aspirin therapy (100–325 mg once daily)
  - Renal dosage adjustment: 1 mg/kg SUB-Q every 24 hours for renal insufficiency (CrCl 10–30 ml/min) —not well studied
- Avoid use in ESRD

Pharmacokinetic Monitoring

Generally, no monitoring. However, anti-Xa units should be measured in special populations (pregnant, severe renal dysfunction, pediatrics, morbidly obese). Goal enoxaparin peak anti-Xa levels (drawn 4 hours postdose at steady state) are usually 0.6–1 IU/ml for twice-daily dosing and probably > 1 IU/ml for once-daily dosing.

Adverse Reactions: Most Common

Bleeding, bruising at injection site

Adverse Reactions: Rare/Severe/Important

HIT type I and type II (lower incidence than with UFH), osteoporosis (with prolonged use, but lower incidence than with UFH), major bleeding (intracranial, retroperitoneal, intraocular)

Major Drug Interactions

Anticoagulants, antiplatelets, thrombolytics: Increase bleeding risk

Contraindications

Active or history of HIT, Active bleeding, not for IM use

Major Drug Interactions

Anticoagulants, antiplatelets, thrombolytics: Increase bleeding risk

Essential Monitoring Parameters

- CBC: Hemoglobin for bleeding and platelets for HIT; serum creatinine due to renal clearance
- Anti-Xa levels in special populations—obesity, pediatrics, pregnancy, and severe renal dysfunction

Counseling Points

- Contact healthcare provider if experiencing bleeding
- Injections are given around the navel or in the upper thigh or buttocks
- Rotate injection sites daily
- Use proper injection technique: Inject under the skin, not into the muscle
- Expect a slight pain during injection and bruising at the injection site

Key Points

- **Black Box Warning:**
  - When neuraxial anesthesia or spinal puncture is employed, patients who are anticoagulated or scheduled to be anticoagulated with LMWHs for prevention of thromboembolic complications are

at risk of developing an epidural or spinal hematoma that can result in long-term or permanent paralysis. Consider benefit versus risk.
- Home use of LMWH is a benefit over UFH. Safe for home use and often employed as a "bridge" to maintenance anticoagulation with warfarin
- Never administer dalteparin or enoxaparin IM due to risk of hematoma
- Protamine sulfate is an antidote but only partially reverses therapeutic effects, Andexanet (AndexXa, Portola Pharmaceuticals) is awaiting approval and should reverse LMWHs.
  - Protamine sulfate (1%): 1 mg for every 1 mg of enoxaparin
  - Protamine sulfate (1%): 1 mg for every 100 units of dalteparin
- Avoid LMWH use in patients with severe renal impairment or very low or high body weight unless anti-Xa monitoring is employed (which is difficult in practice)
- Discontinue treatment doses 24 hours prior to surgery, use a half dose 24 hours before the procedure if taking once daily dosing
- Safe for home use and often employed as a "bridge" to maintenance anticoagulation with warfarin
- May be used in pregnancy (anticoagulant drug of choice), category B, but anti-Xa monitoring is recommended
- Cannot be used in patients with a history of HIT due to risk of reactivation

ANTIPLATELETS, ASPIRIN

Introduction

Aspirin is an oral antiplatelet agent used as an analgesic, antipyretic, anti-inflammatory, and, most commonly, for prevention of cardiovascular events. Aspirin is most commonly used to reduce arterial thrombosis, which may lead to myocardial infarction or stroke in high-risk patients. Aspirin's benefits are tempered by its dose-dependent risk of bleeding, especially gastrointestinal.

Mechanism of Action for the Drug Class

Aspirin irreversibly inhibits the cyclo-oxygenase enzyme, blocking the synthesis of cyclic prostanoids, such as thromboxane A2, prostacyclin, and other prostaglandins. Aspirin's antiplatelet effects are due to the inhibition of thromboxane A2 synthesis, a potent mediator of platelet aggregation and vasoconstriction. Its effects reduce the risk of arterial thrombosis.

Members of the Drug Class

In this section: Aspirin
Others: None

◉ Aspirin

Brand Names

Various

Generic Name

Aspirin

OTC

Dosage Forms

Tablet, chewable tablet, enteric-coated tablet, capsule, caplet, suppository

Usage

Pain; fever; various inflammatory conditions, such as rheumatic fever, rheumatoid arthritis, and osteoarthritis; *cardioprotection (prevention of cerebrovascular accident [CVA] and myocardial infarction [MI]) in high-risk primary prevention patients and in secondary prevention of MI, CVA, or transient ischemic attack (TIA), or following percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)*

Pregnancy Category D

Dosing

- Pain, fever: 325–650 mg PO every 4 to 6 hours, as needed
- Inflammation: 3.6–5.4 g PO daily in divided doses
- TIA/CVA: 75–100 mg PO daily (81 mg PO daily)
- MI/post-PCI/post-CABG: 81–325 mg PO daily

Adverse Reactions: Most Common

Dyspepsia, bleeding

Adverse Reactions: Rare/Severe/Important

GI bleeding (dose dependent), Reye's Syndrome—avoid use in children

Major Drug Interactions

Drugs Affecting Aspirin

- Uricosurics: May decrease effectiveness
- Anticoagulants or concomitant antiplatelets: Increase bleeding risk
- NSAIDs: Increase bleeding risk and may reduce antiplatelet efficacy

Aspirin's Effect on Other Drugs

- Lithium: Increases levels
- Methotrexate: Increases levels
- ACE inhibitors: Decreases effectiveness

Contraindications

- Asthma; rhinitis; nasal polyps—use with caution due to increased risk of salicylate sensitivity
- Inherited or acquired bleeding disorders (including factor VII and factor IX deficiency)
- Do not use in children (< 16 years of age) for viral infections (chickenpox or flu symptoms), with or without fever, due to a potential association with Reye's syndrome
- Pregnancy (third trimester especially)

Counseling Points

- There is an increased risk of bleeding: Monitor for blood in urine and stool and watch for nosebleeds
- Take with food or after meals to reduce GI upset
- Limit alcohol intake

Key Points

- Aspirin's risk of GI ulcers/bleeding is dose dependent and the lowest possible effective dose should be used. Many patients will require ASA with concomitant antiplatelets or anticoagulants—this is acceptable if the benefits outweigh the risks. ASA 81 mg is adequate for optimal cardiovascular benefit for most indications.
- Avoid use in children < 16 years of age due to risk of Reye's syndrome
- Generally, stop 7 days before surgical procedure if discontinuation is deemed necessary

ANTIPLATELETS, ASPIRIN/DIPYRIDAMOLE

Introduction

Aspirin and dipyridamole are oral antiplatelet agents used in combination to reduce stroke risk in patients who have had a transient ischemic attack (TIA) due to thrombosis. Major adverse effects include bleeding and headache.

Mechanism of Action for the Drug Class

Aspirin and dipyridamole have additive antiplatelet effects. Aspirin irreversibly inhibits the cyclo-oxygenase enzyme, blocking the synthesis of cyclic prostanoids, such as thromboxane A2, prostacyclin, and other prostaglandins. Aspirin's antiplatelet effects are due to the inhibition of thromboxane A2 synthesis, a potent mediator of platelet aggregation and vasoconstriction. Dipyridamole decreases platelet aggregation and platelet activation by increasing endogenous concentrations of adenosine and cyclic adenosine monophosphate (cAMP). It reduces the risk of arterial thrombus formation to prevent stroke.

Members of the Drug Class

In this section: Aspirin and dipyridamole
Others: None

◉ Aspirin and Dipyridamole

Brand Name

Aggrenox

Generic Name

Aspirin and dipyridamole

Rx Only

Dosage Form

Capsule, extended release

Usage

Reduce stroke risk in patients who have had a TIA/CVA due to thrombosis

Pregnancy Category D

Dosing

One capsule (dipyridamole 200 mg, aspirin 25 mg) orally twice daily. Avoid use if CrCl < 10 ml/min.

Adverse Reactions: Most Common

Headache, nausea

Adverse Reactions: Rare/Severe/Important

Bleeding

Major Drug Interactions

Drugs Affecting Aspirin

- Uricosurics: May decrease effectiveness
- Anticoagulants or concomitant antiplatelet agents: Increase bleeding risk
- NSAIDs: Increase bleeding risk and may reduce antiplatelet efficacy of aspirin

Aspirin's Effect on Other Drugs

- Lithium: Increases levels
- Methotrexate: Increases levels
- ACE inhibitors: Decreases effectiveness

Drugs Affecting Dipyridamole

Antiplatelets, anticoagulants, NSAIDs: Increase risk of bleeding

Dipyridamole's Effect on Other Drugs

- Adenosine, beta blockers: Increases effect
- Colchicine: Increases serum concentrations. Avoid if patient has impaired renal or hepatic function
- Everolimus: Increases serum concentrations

Contraindications

- Asthma; rhinitis; nasal polyps—use with caution due to increased risk of salicylate sensitivity
- Inherited or acquired bleeding disorders (including factor VII and factor IX deficiency);
- Do not use in children (< 16 years of age) for viral infections (chickenpox or flu symptoms), with or without fever, due to a potential association with Reye's syndrome
- Pregnancy (third trimester especially)

Counseling Points

- Increased risk of bleeding: Monitor for blood in urine and stool and watch for nosebleeds
- Capsule should be swallowed whole; do not crush or chew. May be administered with or without food.
- Limit alcohol intake
- Rise slowly from a sitting/supine position
- This drug may cause a headache. May take up to 1 week for tolerance to headache to develop.

Key Points

- Avoid use in children < 16 years of age due to risk of Reye's syndrome
- Generally, stop 1 week before surgical procedure

ANTIPLATELETS, P2Y12 PLATELET ADENOSINE DIPHOSPHATE (ADP)-RECEPTOR ANTAGONIST

Introduction

The P2Y12 inhibitor antiplatelet agents are used predominantly in combination with aspirin to prevent arterial thrombosis, especially following myocardial infarction (MI) and/or percutaneous coronary intervention (PCI). Ticlopidine has been largely replaced in clinical practice by clopidogrel, prasugrel or ticagrelor because of its increased risk of hematologic adverse effects. Clopidogrel is the most commonly used P2Y12 inhibitor; however, its effectiveness is reduced in patients taking certain medications and in patients who are not able to convert it to the active drug due to genetic variations. Prasugrel and ticagrelor are newly available potent P2Y12 inhibitors. Prasugrel's lack of overall benefit, mainly due to excessive risk of bleeding, in patients with a history of stroke, advanced age, and low body weight limit its use. Ticagrelor's twice-daily dosing and dyspnea side effect limit its use. The major adverse effects of P2Y12 inhibitor antiplatelet agents are bleeding.

Mechanism of Action for the Drug Class

The P2Y12 inhibitors can be classified according to their derivative as either a thienopyridine or non-thienopyridine. The significance of this difference translates to their activity at the P2Y12 platelet receptor. The thienopyridine P2Y12 inhibitors, clopidogrel, prasugrel, and ticlopidine irreversibly inhibit platelet aggregation by selectively and permanently blocking adenosine diphosphate's (ADP) binding to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation to reduce the risk of arterial thrombosis. The non-thienopyridines, ticagrelor, and cangrelor, differ from the thienopyridines in two meaningful ways. 1) They do not require activation to their active metabolites to exert their effects and 2) their binding of ADP to the platelet receptor is reversible, thus allowing for a shorter pharmacodynamic half-life.

Members of the Drug Class

In this section: Clopidogrel, prasugrel, ticagrelor
Others: Ticlopidine, cangrelor

◉ Clopidogrel

Brand Name

Plavix

Generic Name

Clopidogrel

Rx Only

Dosage Form

Tablet

Usage

Reduction of thrombotic events (MI, stroke, and vascular death) in patients with atherosclerosis documented by recent stroke, recent MI, or established peripheral arterial disease (PAD); for patients with acute coronary syndromes (unstable angina/MI), including patients who are to be managed medically and those who are to be managed with PCI or CABG

Pregnancy Category B

Dosing

- Recent MI, recent stroke, or established PAD: 75 mg PO daily
- Acute coronary syndromes, including PCI: 300–600 mg loading dose PO on day 1, then 75 mg PO daily.

Adverse Reactions: Most Common

Bleeding

Adverse Reactions: Rare/Severe/Important

Agranulocytosis

Major Drug Interactions

Drugs Affecting Clopidogrel

Proton pump inhibitors: May decrease effectiveness (controversial)

Clopidogrel's Effect on Other Drugs

Anticoagulants, antiplatelets (i.e., NSAIDs, aspirin): Increases bleeding risk

Contraindications

Active pathologic bleeding, patients who are likely to undergo urgent CABG surgery

Counseling Points

- Adherence is critical post-PCI or post-CABG because in-stent thrombosis and graft thrombosis have a high fatality rate
- Report unusual bleeding, symptoms of dark or bloody urine, or petechiae

Key Points

- **Black Box Warning:**
  - Poor metabolizers of Cytochrome P450 2C19 may have reduced efficacy when taking clopidogrel because they have reduced conversion of the drug to its active metabolite. Tests are available to test for poor metabolizers (although they are not standardized and are rarely used clinically). Consider alternative therapy in poor metabolizers.
- Stop clopidogrel 5 days before elective surgical procedure, may stop > 24 hours before on-pump CABG and off-pump CABG may be performed within 24 hours of dose if benefit outweighs risk

Prasugrel

Brand Name

Effient

Generic Name

Prasugrel

Rx Only

Dosage Form

Tablet

Usage

Reduction of thrombotic events (stent thrombosis) in patients who are to be managed with PCI for acute coronary syndromes (unstable angina/MI)

Pregnancy Category

Not classified. No adverse effects noted in animal models. No experience in pregnant women. Consider bleeding as a risk.

Dosing

Acute "coronary syndromes" undergoing PCI: 60 mg loading dose at time of PCI, then 10 mg orally daily (manufacturer suggests decreasing maintenance dose to 5 mg orally once daily in patients weighing < 60 kg; however, data do not exist to support this recommendation)

Adverse Reactions: Most Common

Bleeding

Adverse Reactions: Rare/Severe/Important

Thrombotic thrombocytopenic purpura, severe bleeding (postprocedural, intraocular, retroperitoneal, intracranial)

Major Drug Interactions

Drugs Affecting Prasugrel

Strong CYP3A4 inhibitors may increase levels and strong CYP3A4 inducers may decrease levels

Prasugrel's Effect on Other Drugs

Anticoagulants, antiplatelets (i.e., NSAIDs, aspirin): Increases bleeding risk

Contraindications

Active pathologic bleeding; history of TIA or CVA; patients ≥ 75 years (may be considered in high-risk situations, such as patients with diabetes or history of MI); patients < 60 kg due to increased bleeding risk—consider lower maintenance dose, patients who are likely to undergo urgent CABG surgery

Counseling Points

- Adherence is critical post-PCI or post-CABG because in-stent thrombosis or graft thrombosis has a high fatality rate
- Report unusual bleeding, symptoms of dark or bloody urine, or petechiae

Key Points

- **Black Box Warning:**
  - Prasugrel has a risk of bleeding. Avoid use if patient is > 75 years old (unless high risk), has a history of TIA/CVA or if the patient may need emergent CABG. Consider avoiding use in patients who are higher bleeding risk including: < 60 kg, propensity to bleed or concomitant antiplatelet or anticoagulant agents. Suspect bleeding in hypotensive patients who have recently had an invasive procedure. Attempt to continue prasugrel to prevent cardiac events, if bleeding occurs.
- Prasugrel is often considered to be more potent than clopidogrel but may have an unacceptable bleeding risk in certain patients, as noted in the Black Box Warning

◉ Ticagrelor

Brand Name

Brilinta

Generic Name

Ticagrelor

Rx Only

Dosage Form

Tablet

Usage

Reduction of thrombotic events (cardiovascular death, myocardial infarction, stroke) in patients with acute coronary syndromes (unstable angina/MI) who are to be managed medically or interventionally with PCI or CABG

Pregnancy Category C

Dosing

Acute "coronary syndromes" undergoing PCI: 180 mg loading dose at time of PCI, then 90 mg orally BID

Adverse Reactions: Most Common

Dyspnea, bleeding

Adverse Reactions: Rare/Severe/Important

Thrombotic thrombocytopenic purpura, severe bleeding (postprocedural, intraocular, retinal, retroperitoneal, intracranial)

Major Drug Interactions

Drugs Affecting Ticagrelor

- Avoid Strong CYP3A4 inhibitors, as these may increase ticagrelor drug exposure and the risk for dyspnea and bleeding (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, protease inhibitors)
- Avoid strong CYP3A4 inducers, as these may significantly decrease drug exposure and efficacy (e.g., rifampin, phenytoin, carbamazepine, and phenobarbital)
- Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor and should be avoided

Ticagrelor's Effect on Other Drugs

- Anticoagulants, antiplatelets (i.e., NSAIDs, aspirin): Increases bleeding risk

Contraindications

History of intracranial bleeding, active pathologic bleeding, such as peptic ulcer or intracranial hemorrhage

Counseling Points

- Adherence is critical post-PCI or post-CABG because in-stent thrombosis or graft thrombosis has a high fatality rate
- Report unusual bleeding, symptoms of dark or bloody urine, or petechiae
- Report any new or unexpected of shortness of breath

Key Points

- **Black Box Warnings:**
  - To reduce bleeding risk, do not use ticagrelor in the following patients: active bleeding, history of intracranial hemorrhage, patients undergoing urgent CABG. When possible, manage bleeding without drug discontinuation due to risk of arterial thrombosis.
  - Avoid concomitant ASA doses > 100 mg daily as they decrease the effectiveness of ticagrelor
- Ticagrelor is often considered to be more potent than clopidogrel but may have an unacceptable bleeding risk in certain patients.
- Ticagrelor is often used in combination with aspirin therapy but concomitant aspirin doses must be < 100 mg/day as higher doses may reduce the effectiveness of ticagrelor.
- Ticagrelor should be stopped 5 days before a surgical procedure

PHOSPHODIESTERASE III INHIBITORS

Introduction

Cilostazol is a phosphodiesterase inhibitor used most commonly for treatment of claudication caused by peripheral vascular disease. Cilostazol is an antiplatelet agent and an arterial vasodilator. The most common adverse effect is headache.

Mechanism of Action

Cilostazol inhibits phosphodiesterase III activity and suppresses cAMP degradation, which increases cAMP in platelets and blood vessels, leading to reversible inhibition of platelet aggregation and vasodilation. Therefore, cilostazol is both an antiplatelet agent and an arterial vasodilator.

Members of the Drug Class

In this section: Cilostazol
Others: None

◉ Cilostazol

Brand Name

Pletal

Generic Name

Cilostazol

Rx Only

Dosage Form

Tablets

Usage

To reduce intermittent claudication and improve walking distance, in patients with peripheral vascular disease; prevention of stroke, prevention of stent thrombosis

Pregnancy Category C

Dosing

Intermittent Claudication: 100 mg PO BID taken at least 30 minutes before or 2 hours after breakfast and dinner
Reduce dose to 50 mg PO BID if significant drug interactions exist (see Drug Interactions section)

Adverse Reactions—Most Common

Tachycardia/palpitations, hypotension, headache, diarrhea

Adverse Reactions—Rare/Severe/Important

Bleeding, thrombocytopenia, or leukopenia progressing to agranulocytosis, Tachyarrhythmias

Major Drug Interactions

- CYP3A4 inhibitors (ketoconazole, itraconazole, erythromycin, and diltiazem) or CYP2C19 inhibitors (ticlopidine, fluconazole, and omeprazole)—Reduce dose to 50 mg PO BID
- Antiplatelet or anticoagulant agents—Potential increased risk of bleeding

Contraindications

HF class, all severities

Essential Monitoring Parameters

- Symptoms of intermittent claudication and walking distance to evaluate efficacy
- CBC periodically: Monitor platelets and white blood cells and discontinue drug immediately if leukopenia or thrombocytopenia develops to prevent agranulocytosis
- Blood pressure and heart rate due to adverse effects of tachycardia and hypotension

Counseling Points

- You must take this medication 30 minutes before or 2 hours after a meal as food (especially a high-fat meal) increases drug levels
- This medication is being prescribed to treat symptoms of leg pain while you are walking due to your compromised circulation if you have peripheral vascular disease (PVD). If this medication does not improve your symptoms, you should talk to your healthcare provider about discontinuing it.
- Let your healthcare provider know if you begin any new medications, including herbals or OTC medications, as your dose may need to be decreased or there may be an increased risk of side effects

Key Points

- **Black Box Warning:**
  - Avoid use in patients with HF of any severity. Phosphodiesterase III inhibitors have demonstrated increased mortality in patients with class III-IV HF.
- Cilostazol is one of the few medications that may reduce the symptoms of claudication. Discontinue therapy if no response in symptoms of PVD.
- This medication must be separated from meals (30 minutes before or 2 hours after a meal) to prevent supratherapeutic drug levels
- Cilostazol will accumulate and lead to increased adverse effects in patients taking medications that inhibit CYP3A4 or CYP2C19 (listed in drug interactions above). Reduce dose to 50 mg twice daily in patients taking these medications concomitantly.

THROMBOLYTICS

Introduction

Thrombolytics, such as alteplase, are the only agents available that can dissolve formed pathologic clots. These agents mimic the endogenous fibrinolytic system. These injectable agents are indicated in certain life-threatening situations, such as myocardial infarction (MI), cerebrovascular accident (CVA), massive pulmonary embolism, and critical limb ischemia, where their benefit outweighs their significant risk of life-threatening bleeding.

Mechanism of Action for the Drug Class

Alteplase is a tissue plasminogen activator produced by recombinant DNA technology. Alteplase has high affinity to fibrin-bound plasminogen that stimulates the conversion of plasminogen to plasmin, which lyses (breaks apart) clots by breaking down fibrin and fibrinogen contained in a formed clot

Members of the Drug Class

In this section: Alteplase
Others: Defibrotide, reteplase, tenecteplase, urokinase, streptokinase, anistreplase

◉ Alteplase

Brand Name

Activase

Generic Names

Alteplase, recombinant or tissue plasminogen activator (TPA)

Rx Only

Dosage Form

IV injection

Usage

Acute MI, acute ischemic stroke, pulmonary embolism, peripheral arterial thromboembolism, central venous catheter occlusion

Pregnancy Category C

Dosing

- Acute MI:
  - Accelerated infusion:
    - If weight > 67 kg: 15 mg IV bolus, 50 mg infused IV over 30 minutes, then 35 mg infused IV over 60 minutes
    - If weight ≤ 67 kg: 15 mg IV bolus, 0.75 mg/kg infused IV over 30 minutes (not to exceed 50 mg), then 0.50 mg/kg infused IV over 60 minutes (not to exceed 35 mg)
  - Three-hour infusion: 100 mg given as 60 mg infused IV in the first hour, 20 mg infused IV over the second hour, and 20 mg infused IV over the third hour. For smaller patients (< 65 kg), use a dose of 1.25 mg/kg infused IV over 3 hours, as described.
- Acute ischemic stroke: 0.9 mg/kg (not to exceed 90 mg) infused IV over 60 minutes with 10% of the total dose administered as an initial IV bolus over 1 minute
- Pulmonary embolism: 100 mg infused IV over 2 hours
- Catheter occlusion: 2 mg/2 ml instilled into occluded catheter; up to 2 doses may be used

Adverse Reactions: Most Common

Bleeding

Adverse Reactions: Rare/Severe/Important

Major bleeding (intracranial, retroperitoneal, intraocular)—much higher risk than with anticoagulants

Major Drug Interactions

Drugs Affecting Alteplase/TPA

Anticoagulants, antiplatelets: Increase bleeding risk

Contraindications

Screening of these is critical to reduce the risk of life-threatening bleeding; active internal bleeding, CVA within 2 to 3 months, head trauma or intracranial/intraspinal surgery, intracranial abnormalities that increase bleeding risk (i.e. neoplasm), known bleeding diatheses, including current anticoagulant use (INR > 1.7 or use of direct oral anticoagulants with elevated sensitive laboratory tests), severe uncontrolled HTN of > 185/110 (control prior to lytic administration), suspected aortic dissection

Essential Monitoring

CBC, fibrinogen

Counseling Point

This medication has a life-threatening bleeding risk, especially intracranial bleeding. Thrombolytics should only be considered in emergency situations where the benefit outweighs the bleeding risk.

Key Points

- Most beneficial if given within 12 hours of onset of MI symptoms or within 3 hours of onset of stroke symptoms. May be given within 3 to 4.5 hours of onset of stroke symptoms in select patients.
- There is an extensive list of contraindications and precautions that must be considered. These indicate situations where the risk of life-threatening bleeding may outweigh the benefit of therapy.

COLONY-STIMULATING FACTORS

Introduction

Filgrastim and pegfilgrastim are colony-stimulating factors used most commonly for the prevention and treatment of neutropenia in cancer and HIV patients. Pegfilgrastim is a pegylated form of filgrastim with a longer duration of action. Their most common adverse effect is bone pain.

Mechanism of Action for the Drug Class

Filgrastim and pegfilgrastim are human granulocyte colony-stimulating factors (G-CSFs), which are produced by recombinant DNA technology. Endogenous G-CSF is a lineage-specific, colony-stimulating factor that is produced by monocytes, fibroblasts, and endothelial cells. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation. Pegfilgrastim has a longer duration of action than filgrastim.

Members of the Drug Class

In this section: Filgrastim, pegfilgrastim
Others: Eltrombopag, romiplostim, sargramostim

◉ Filgrastim

Brand Name

Neupogen, Granix (tbo-filgrastim), Zarxio (filgrastim-sndz)

Generic Name

Filgrastim

Rx Only

Dosage Forms

Injection (IV, SUB-Q)

Usage

- *Myelosuppressive chemotherapy: Decreases incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia and fever*
- *Bone marrow transplantation (BMT): Reduces duration of neutropenia and neutropenia-associated sequelae in patients with nonmyeloid malignancies undergoing myeloablative therapy followed by BMT*
- *Peripheral blood progenitor cell (PBPC) collection and therapy in cancer patients: Mobilizes hematopoietic progenitor cells into the peripheral blood for leukapheresis collection*
- *Patients with severe chronic neutropenia (SCN): Chronic administration reduces the incidence and duration of sequelae of neutropenia in symptomatic patients with congenital, cyclic, or idiopathic neutropenia*
- *Treatment of neutropenia in patients with human immunodeficiency virus (HIV)*

Pregnancy Category C

Dosing

- Myelosuppressive chemotherapy: Initial dose of 5 µg/kg/day SUB-Q daily, short IV infusion (15–30 minutes), or continuous SUB-Q or IV infusion
- BMT: 10 µg/kg/day IV infusion of 4 or 24 hours or 24-hour SUB-Q infusion
- PBPC: 10 µg/kg/day SUB-Q, either as a bolus or continuous infusion
- SCN:
  - Congenital neutropenia: 6 µg/kg SUB-Q twice daily
  - Idiopathic or cyclic neutropenia: 5 µg/kg SUB-Q daily
- HIV with neutropenia: 5–10 µg/kg per day SUB-Q for 2 to 4 weeks

◉ Pegfilgrastim

Brand Name

Neulasta, Neulasta Onpro

Generic Name

Pegfilgrastim

Rx Only

Dosage Form

Injection (SUB-Q)

Usage

- *Myelosuppressive chemotherapy: Decreases incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia and fever*
- To increase survival in patients acutely exposed to myelosuppressive doses of radiation therapy

Pregnancy Category C

Dosing

- Myelosuppressive chemotherapy: Initial dose: 6 mg SUB-Q once per chemotherapy cycle
- Postradiation therapy: 6 mg SUB-Q x 2 doses 1 week apart

Adverse Reactions: Most Common

Bone pain, reversible elevations in uric acid, lactate hydrogenase, alkaline phosphatase, nausea, vomiting

Adverse Reactions: Rare/Severe/Important

Hypersensitivity, splenic rupture, acute respiratory distress syndrome (ARDS), sickle cell crisis

Major Drug Interactions

Drugs Affecting Filgrastim/Pegfilgrastim

Lithium: May potentiate release of neutrophils

Contraindications

No notable contraindications

Essential Monitoring Parameter

Neutrophil count is monitored to assess response to therapy

Counseling Point

Advise on proper dosage and administration

Key Points

- Nonnarcotic analgesics relieve bone pain
- Round dose to nearest full vial or prefilled syringe
- Do not administer 14 days before to 24 hours after administration of cytotoxic chemotherapy

ERYTHROPOIETINS, RECOMBINANT HUMAN

Introduction

Epoetin alfa and darbepoetin alfa are both injections used to treat anemia. Darbepoetin alfa has a longer duration of action.

Mechanism of Action for the Drug Class

Erythropoietin is a glycoprotein that stimulates red blood cell production. Endogenous erythropoietin is produced in the kidneys and stimulates the division and differentiation of committed erythroid progenitors in the bone marrow. Epoetin alfa and darbepoetin alfa are made by recombinant DNA technology and have the same biological effects as endogenous erythropoietin. Darbepoetin alfa has a longer terminal half-life than epoetin alfa. The most common adverse effect is hypertension.

Members of the Drug Class

In this section: Epoetin alfa, darbepoetin alfa

◉ Epoetin Alfa

Brand Names

Epogen, Procrit

Generic Name

Epoetin alfa

Rx Only

Dosage Forms

Injection (IV, SUB-Q)

Usage

Treatment of anemia associated with chronic renal failure (CRF), treatment of anemia in cancer patients on chemotherapy, treatment of anemia related to zidovudine therapy in HIV, reduction of allogeneic blood transfusion in surgery patients

Pregnancy Category C

Dosing

- CRF on dialysis:
  - Initial dose: 50–100 units/kg 3 times weekly IV (preferred) or SUB-Q
  - Maintenance dose: Individualize dose to target Hgb (not to exceed 11 g/dl)
- CRF not on dialysis:
  - Initial dose: 50–100 units/kg 3 times weekly IV or SUB-Q
  - Maintenance dose: Individualize dose to target Hgb (not to exceed 10 g/dl)
- HIV:
  - Initial dose: 100 units/kg IV or SUB-Q 3 times weekly for 8 weeks
  - Maintenance dose: Increase dosages in 50–100 units/kg increments to achieve target Hgb (not to exceed 12 g/dl)
  - Maximum dose: 300 units/kg dose 3 times weekly
- Cancer patients:
  - Initial dose: 150 units/kg SUB-Q 3 times weekly
  - Maximum dose: 300 units/kg doses 3 times weekly
- Surgery:
  - 300 units/kg per day SUB-Q for 10 days before surgery and for 4 days after surgery *or*
  - 600 units/kg SUB-Q in once-weekly doses 21, 14, and 7 days before surgery plus a fourth dose on the day of surgery

Darbepoetin Alfa

Brand Name
Aranesp

Generic Name
Darbepoetin alfa

Rx Only

Dosage Form
Injection (IV or SUB-Q)

Usage
Treatment of anemia associated with CRF, treatment of anemia in cancer patients on chemotherapy

Pregnancy Category C

Dosing
- CRF on dialysis:
  - Initial dose: 0.45 µg/kg as single IV or SUB-Q injection once weekly *or*
  - 0.75 µg/kg as single IV or SUB-Q injection every 2 weeks
  - Maintenance dose: Individualize dose to target Hgb (not to exceed 11 g/dl)
- CRF not on dialysis:
  - Initial dose: 0.45 µg/kg SUB-Q once every 4 weeks
  - Maintenance dose: Individualize dose to target Hgb (not to exceed 10 g/dl)
- Cancer patients:
  - Initial dose:
    - 2.25 µg/kg SUB-Q weekly *or*
    - 500 µg SUB-Q every 3 weeks
  - Maximum dose: Individualize dose to maintain a Hgb level sufficient to avoid red blood cell transfusions

Adverse Reactions: Most Common
Hypertension, headache, tachycardia, nausea, vomiting, diarrhea, shortness of breath, hyperkalemia

Adverse Reactions: Rare/Severe/Important
Hypertension, hypersensitivity, thrombosis, seizures

Major Drug Interactions
None

Contraindications
Uncontrolled hypertension, pure red cell aplasia that begins after treatment with epoetin alfa

Counseling Points
- Advise of proper dosage and administration
- Be aware of the signs and symptoms of an allergic drug reaction and take appropriate action, if necessary
- Do not reuse needles, syringes, or drug products and dispose of them properly

Key Points
- **Black Box Warning:**
  - May increase the risk of death, MI, CVA, DVT/PE thrombosis of vascular access and tumor progression or recurrence. Discontinue use if hemoglobin > 11 g/dl in CKD patients. In cancer patients, discontinue epoetin when chemotherapy is completed and note that therapy is not indicated in patient receiving myelosuppressive therapy with a goal of cancer cure. DVT prophylaxis is indicated perioperatively due to increased risk with this medication.
- Approximately 2 to 6 weeks for clinically significant change in Hgb
- Iron stores should be assessed and iron supplementation given, as needed
- Physicians need to be registered in the ESA APPRISE Oncology Program to prescribe and/or dispense epoetin alfa or darbepoetin alfa for anemia in cancer patients on chemotherapy

REVIEW QUESTIONS

1. Which of the following is the correct monitoring test for warfarin?
   - **a.** PT/INR
   - **b.** aPTT
   - **c.** Anti-Xa level
   - **d.** BMP

2. Which of the following medications interacts with warfarin and would DECREASE the PT/INR?
   - **a.** Fluconazole
   - **b.** Rifampin
   - **c.** Ibuprofen
   - **d.** Amiodarone

3. The brand name for rivaroxaban is:
   a. Eliquis
   b. Xarelto
   c. Savaysa
   d. Cordarone

4. Rivaroxaban should be AVOIDED in a patient with:
   a. A mechanical prosthetic cardiac valve
   b. A proximal DVT
   c. Atrial fibrillation
   d. A recent total hip replacement

5. The antidote for the direct Xa inhibitors, rivaroxaban and apixaban, which is awaiting approval is:
   a. Protamine
   b. Phytonadione
   c. Andexanet Alfa
   d. Praxbind

6. The mechanism of action of apixaban is:
   a. To prevent carboxylation of clotting factors II, VII, IX and X
   b. To directly inhibit active clotting factor Xa
   c. To inhibit clotting factors Xa and IIa by increasing the activity of antithrombin
   d. To inhibit thromboxane A2 synthesis to exert antiplatelet effects

7. A critical counseling point for rivaroxaban is that:
   a. It must be taken on an empty stomach
   b. Doses must be administered 8 hours apart
   c. It must be taken with food to optimize efficacy
   d. It is always taken twice daily

8. Which of the following is an INCORRECT dose of aspirin for cardiovascular protection?
   a. 81mg PO daily
   b. 162 mg PO daily
   c. 325 mg PO daily
   d. 650 mg PO BID

9. In which of the following concomitant conditions is cilostazol contraindicated?
   a. HF
   b. HTN
   c. Atrial fibrillation
   d. PVD

10. Which of the following is the MOST COMMON adverse effect in patients taking Aggrenox?
   a. Headache
   b. Hypertension
   c. Dysuria
   d. Shortness of breath

11. Currently, the most commonly used thienopyridine medication in the United States is:
   a. Ticlopidine
   b. Prasugrel
   c. Clopidogrel
   d. Ticagrelor

12. The brand name for clopidogrel is:
   a. Plavix
   b. Effient
   c. Aggrenox
   d. Xarelto

13. Which of the following patients SHOULD NOT receive prasugrel therapy due to increased bleeding risk (based on the information provided)?
   a. A 60-year-old patient with recent MI
   b. An 80-year-old patient with history of CVA
   c. An 85 kg patient who is post-PCI
   d. A 65 kg patient who is post-MI

14. A rare but severe adverse effect of Effient is:
   a. Thrombotic thrombocytopenic purpura
   b. Anemia
   c. Hypertensive urgency
   d. Brugada syndrome

15. Filgrastim is a(n):
   a. Glycoprotein, which stimulates red blood cell production
   b. Granulocyte colony-stimulating factor, which regulates neutrophil production in the bone marrow
   c. Antiplatelet agent, which blocks synthesis of thromboxane A2
   d. Anticoagulant agent, which prevents carboxylation of clotting factors II, VII, IX, and X

16. What is an indication for Neupogen?
   a. Febrile neutropenia in patients with HIV
   b. Anemia in patients with CKD
   c. Post-PCI in a patient with MI
   d. Hemorrhagic CVA

17. Which of the following is FALSE about Neulasta?
   a. It is administered as an intravenous infusion
   b. It has the same mechanism of action as Neupogen but a longer duration of action
   c. A common adverse effect is bone pain
   d. Its generic name is pegfilgrastim

18. Which of the following is a monitoring parameter for Epogen?

- **a.** Neutrophil count
- **b.** Hemoglobin
- **c.** INR
- **d.** Platelet count

19. Which of the following is a Black Box Warning in the prescribing information for Epoetin Alfa?

- **a.** Avoid use in patients with CrCl< 30 ml/min due to risk of anemia
- **b.** DVT prophylaxis is indicated perisurgery due to increased risk with this medication
- **c.** Avoid use in patients with hypotension due to risk of syncope
- **d.** Patients receiving oral therapy with epoetin alfa may experience GI bleeding

20. The antidote for UFH is:

- **a.** Phytonadione
- **b.** Idarucizumab
- **c.** Protamine
- **d.** Andexanet alfa

21. A life-threatening adverse effect of UFH is:

- **a.** Bruising at the injection site
- **b.** Seizures
- **c.** HIT
- **d.** Bradycardia

22. Which of the following is a CORRECT route of administration for enoxaparin?

- **a.** PO
- **b.** IM
- **c.** SQ
- **d.** Sublingual

23. Lovenox is pregnancy category:

- **a.** A
- **b.** B
- **c.** C
- **d.** X

24. The generic name for Fragmin is:

- **a.** Apixaban
- **b.** Bivalirudin
- **c.** Filgrastim
- **d.** Dalteparin

25. A monitoring test used for bivalirudin is:

- **a.** INR
- **b.** aPTT
- **c.** Prothrombin time
- **d.** Bivalirudin drug levels

26. Angiomax's mechanism of action is a:

- **a.** Direct thrombin inhibitor
- **b.** Direct Xa inhibitor
- **c.** Inhibitor of thromboxane A2 synthesis
- **d.** Thrombolytic

27. A common side effect of Pradaxa is:

- **a.** Hypertension
- **b.** Dyspepsia
- **c.** Constipation
- **d.** Headache

28. All of the following are important patient counseling points for dabigatran EXCEPT:

- **a.** Keep medication in original bottle; discard 4 months after opening original container
- **b.** Capsules must be swallowed whole. Do not break, chew, or open capsules
- **c.** Take without regard to meals (but taking with meals may decrease dyspepsia)
- **d.** Immediately discontinue use if stomach upset occurs

29. Alteplase is indicated for all of the following EXCEPT:

- **a.** Acute MI
- **b.** Acute CVA
- **c.** Pulmonary Embolism
- **d.** Distal DVT

30. Which of the following is a CONTRAINDICATION to Alteplase therapy?

- **a.** Current warfarin therapy with INR 2.1
- **b.** Hypotension with BP < 100/50
- **c.** Acute MI
- **d.** History of ischemic CVA 6 years ago

CHAPTER 10

Lipid-Lowering Agents

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BILE ACID SEQUESTRANTS

Introduction

The three bile acid sequestrants (BASs) on the market are cholestyramine, colestipol, and colesevelam. The primary effect of these agents at optimal doses is to reduce LDL by 15% to 30%. In clinical practice, cholestyramine and colestipol are underused due to GI side effects and classic drug-binding interactions of concomitantly administered drugs. Colesevelam is much better tolerated and has fewer drug-binding interactions and thus is generally the preferred agent in this class. These agents are contraindicated in patients with complete biliary obstruction and bowel obstruction. BASs may increase triglycerides; therefore, these agents should generally be avoided in patients with TGs > 400 mg/dl.

Mechanism of Action for the Drug Class

Cholesterol is the precursor of bile acids, which are needed for emulsifying fat and lipid particles in food. Bile acids are secreted into the intestine through the bile, and most bile acids are reabsorbed into the intestines and returned to the liver by enterohepatic circulation. BASs bind to bile acids in the gut, which interrupts recycling through enterohepatic recirculation. Hepatic cells convert more cholesterol into bile acid, and there is an increased synthesis of LDL receptors, leading to increased hepatic uptake of systemic LDL particles and lowered LDL.

Members of the Drug Class

In this section: Cholestyramine
Others: Colesevelam, colestipol

◉ Cholestyramine

Brand Names

Prevalite, Questran, Questran Light

Generic Name

Cholestyramine

Rx Only

Dosage Form

Powder for oral suspension

Usage

Adjunct to diet in the management of primary hypercholesterolemia, *pruritus associated with elevated levels of bile acids, diarrhea associated with excess fecal bile acids, binding of toxicologic agents, adjunctive therapy for pseudomembranous colitis*

Pregnancy Category C

Dosing

- Initial dose: 4 g once or twice daily
- Dosage adjustment: Increase gradually over ≥ 1-month intervals until maintenance dose of 8–16 g a day divided into 2 doses is reached
- Maximum dose: 24 g daily
- Renal dosage adjustment: Because BASs are not systemically absorbed, renal dosage adjustment is not necessary
- Hepatic dosage adjustment: Because BASs are not systemically absorbed, hepatic dosage adjustment is not necessary

Adverse Reactions: Most Common

Constipation (increases with dose and age of the patient); other GI-related adverse reactions include abdominal pain, flatulence, nausea, vomiting, dyspepsia, and steatorrhea

Adverse Reactions: Rare/Severe/Important

Theoretically, patients taking BASs may be at an increased risk of bleeding from hypoprothrombinemia (secondary to vitamin K deficiency)

Major Drug Interactions

Cholestyramine's Effect on Other Drugs

Delays or reduces the absorption of many drugs when administered concomitantly. To avoid this drug interaction, in general, give other medications 1 hour before or 4 to 6 hours after giving BASs. (Note that colesevelam does have a decreased frequency for causing these interactions.) The absorption of the following drugs may be delayed or reduced by cholestyramine (this list is not all-inclusive): Amiodarone, corticosteroids, digoxin, ezetimibe, fat soluble vitamins (vitamins A, D, E, and K), gemfibrozil, HMG-CoA

inhibitors, methyldopa, methotrexate, niacin, NSAIDs, propranolol (and potentially other beta blockers), sulfonylureas, thyroid hormones, thiazide and loop diuretics, thiazolidinedione, valproic acid, and warfarin.

Contraindications

Complete biliary obstruction

Essential Monitoring Parameters

Fasting lipid profile before initiating treatment, 3 months after initiation (within 4 to 6 weeks if baseline fasting triglycerides of 250–299 mg/dl), and every 6 to 12 months thereafter

Counseling Points

- Cholestyramine oral suspension packets should be mixed with 4 to 6 oz of beverage. May also be mixed with highly fluid soups, cereals, applesauce, or pulpy fruits. To decrease the occurrence of flatulence, mix cholestyramine with noncarbonated pulpy juices and swallow it without engulfing air by using a straw.
- Separate the administration of other drugs by 1 hour before or 4 to 6 hours after cholestyramine

Key Points

- Patients should be counseled on drug-binding interactions and to separate dosing of other drugs from cholestyramine. GI-related adverse effects and the palatability of the drug may limit the use of the drug long term.
- Cholestyramine Light formulations contain 14 g of phenylalanine per 5 g dose of cholestyramine

CHOLESTEROL ABSORPTION INHIBITORS

Introduction

Ezetimibe is the only agent available in this class. It is specifically used in combination with a statin to lower LDL. An additional lowering of approximately 25% in LDL can be seen when ezetimibe is combined with a statin, which makes it an attractive add-on agent to reach a lower LDL goal of < 70 mg/dl. Ezetimibe has been proven to be effective in combination with statins in patients unable to achieve or sustain target LDL levels on a statin alone or to reduce the dose of a statin required to achieve target levels. Evidence is emerging regarding lowering of cardiovascular events with ezetimibe treatment. (See the Vytorin section.)

Mechanism of Action for the Drug Class

Ezetimibe inhibits absorption of cholesterol at the brush border of the small intestine via the sterol transporter Niemann-Pick C1-Like1, leading to decreased delivery of cholesterol to the liver, reduction of hepatic cholesterol stores, and increased clearance of cholesterol from the blood

Members of the Drug Class

In this section: Ezetimibe
Others: None

◉ Ezetimibe

Brand Name

Zetia

Generic Name

Ezetimibe

Rx Only

Dosage Form

Tablet

Usage

Used as monotherapy or in combination with HMG-CoA reductase inhibitors for primary heterozygous familial and nonfamilial hypercholesterolemia (in combination with dietary therapy), mixed hyperlipidemia (in combination with fenofibrate), homozygous familial hypercholesterolemia (in combination with atorvastatin or simvastatin), homozygous sitosterolemia

Pregnancy Category C

Dosing

- 10 mg daily without regard to meals
- Renal dosage adjustment: None required for renal insufficiency
- Hepatic dosage adjustment:
  - Mild hepatic insufficiency: No adjustment necessary
  - Moderate-to-severe hepatic impairment: Use not recommended

Adverse Reactions: Most Common

When compared with placebo, ezetimibe is well tolerated. The most common side effects are abdominal pain, diarrhea, arthralgia, cough, fatigue, and headache.

Adverse Reactions: Rare/Severe/Important

Hypersensitivity reactions (including angioedema and rash), increased LFTs, drug-induced myopathy (very rarely with monotherapy), rhabdomyolysis (very rarely

with monotherapy; the risk is increased in combination with a statin)

Major Drug Interactions

Drugs Affecting Ezetimibe

- Bile acid sequestrants: May decrease bioavailability; administer ezetimibe 2 hours before or 4 hours after bile acid sequestrants
- Cyclosporine: May increase serum levels. No monitoring is recommended for ezetimibe.
- Fibrates: May increase cholesterol excretion into the bile, leading to cholelithiasis

Ezetimibe's Effect on Other Drugs

- Cyclosporine: May increase serum levels. Cyclosporine levels should be monitored.

Essential Monitoring Parameters

Total cholesterol profile prior to therapy, and when clinically indicated and/or periodically thereafter. When used in combination with fenofibrate, monitor LFTs and signs and symptoms of cholelithiasis.

Counseling Points

- Take at the same time every day, without regard for meals
- Report allergic reactions: Itching/hives, swelling in the face/hands, trouble breathing (angioedema)
- Report any muscle pain, tenderness, or weakness
- Report nausea, vomiting, loss of appetite, pain in the upper stomach (cholelithiasis)
- Use in conjunction with diet and exercise

Key Points

- In combination with a statin, LDL is lowered by approximately an additional 25%
- Ezetimibe should not be prescribed as a first-line agent

COMBINATION PRODUCT, VYTORIN

Introduction

The combination product Vytorin contains simvastatin and ezetimibe. Until recently, there was lack of meaningful clinical outcome data regarding the use of Vytorin. With the publication of the Study of Heart and Renal Protection (SHARP) trial, Vytorin has been shown to be effective in reducing the risk of vascular events in patients with moderate-to-severe chronic kidney disease (CKD) and no history of myocardial infarction (MI) or coronary revascularization. More recently, the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), showed a modest benefit of combination therapy, simvastatin plus ezetimibe, vs simvastatin monotherapy in acute coronary syndrome patients for reduction in myocardial infarction and stroke over a median follow up of 6 years.

Mechanism of Action for the Drug Class

See the ezetimibe and statin sections

Members of the Drug Class

In this section: Ezetimibe/simvastatin (Vytorin)
Others: None

◉ Ezetimibe/Simvastatin

Brand Name

Vytorin

Generic Name

Ezetimibe/simvastatin

Rx Only

Dosage Form

Tablet

Usage

Used in combination with dietary modification for the treatment of primary hypercholesterolemia and homozygous familial hypercholesterolemia; *Primary and secondary prevention of ASCVD according to the American College of Cardiology/American Heart Association*; Limitations of use: No incremental benefit of ezetimibe/simvastatin on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established. Ezetimibe/simvastatin has not been studied in Fredrickson type I, III, IV, and V dyslipidemias.

Pregnancy Category X

Dosing

- Homozygous familial hypercholesterolemia: 10/40 mg ezetimibe/simvastatin once daily in the evening
- Hyperlipidemias:
  - Initial dose:
    - 10/10–20 mg ezetimibe/simvastatin once daily in the evening
    - Patients who require less aggressive reduction in LDL-C: 10/10 mg ezetimibe/simvastatin once daily in the evening
    - Patients who require > 55% reduction in LDL-C: 10/40 mg ezetimibe/simvastatin once daily in the evening

- Dosing range: 10/10–40 mg ezetimibe/simvastatin once daily
- Dosage adjustment: In Chinese patients on niacin doses ≥ 1 g daily, use caution with simvastatin doses exceeding 20 mg PO daily because of an increased risk of myopathy. Do not administer simvastatin 80 mg.

Adverse Reactions: Most Common

See the ezetimibe and statin sections

Adverse Reactions: Rare/Severe/Important

See the ezetimibe and statin sections

Major Drug Interactions

- Strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, cobicistat-containing products, boceprevir, telaprevir, nefazodone), gemfibrozil, cyclosporine, danazol: Concomitant use is contraindicated
- Verapamil, diltiazem: Do not exceed 10/10 mg ezetimibe/simvastatin daily
- Amiodarone, amlodipine, ranolazine: Do not exceed 10/20 mg ezetimibe/simvastatin daily
- Grapefruit juice: Avoid large quantities of grapefruit juice (> 1 quart daily)
- Other lipid-lowering medications: Use with other fibrate products or lipid-modifying doses (≥ 1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with ezetimibe/simvastatin.

Contraindications

See individual drug sections for simvastatin and ezetimibe

Essential Monitoring Parameters

Liver function tests are required at baseline and as clinically indicated. Consider creatine kinase at baseline and with dosage increases; closely monitor in those with moderate to severe renal impairment receiving doses higher than 10/20 mg ezetimibe/simvastatin.

Counseling Points

- Report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever
- Report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice
- Women of childbearing age should be advised to use an effective method of birth control to prevent pregnancy while using ezetimibe/simvastatin

Key Points

- Ezetimibe monotherapy has produced relatively moderate reductions in LDL cholesterol in patients with primary hypercholesterolemia (less than that of statins). However, studies have shown that the addition of ezetimibe to statin therapy produces greater reductions in LDL cholesterol than monotherapy with either agent alone.
- The combination of ezetimibe and simvastatin presents sufficient dose options to achieve desired treatment goals while providing greater convenience to the patient, therefore, potentially increasing compliance
- Available in four combinations of ezetimibe/simvastatin: 10/10 mg, 10/20 mg, 10/40 mg, and 10/80 mg

FIBRIC ACID DERIVATIVES

Introduction

Fibric acid derivatives are mainly used for the treatment of hypertriglyceridemia. Fenofibrate and gemfibrozil belong to this class. Fenofibrate is the preferred agent when used in combination with statins due to the potential for fewer drug interactions. These drugs are contraindicated in patients with severe renal or hepatic disease, including primary biliary cirrhosis, unexplained persistent elevated liver function abnormality, and preexisting gallbladder disease. The study, Action to Control Cardiovascular Risk in Diabetes (ACCORD)—Lipids, found no evidence of clinically significant benefit for addition of fenofibrate to statins. Based on these findings, on April 18, 2016, the U.S. Food and Drug Administration (FDA) announced retraction of prior approvals related to coadministration of statins with fenofibric acid delayed release capsules.

Mechanism of Action for the Drug Class

The mechanism of action of fibric acid derivatives is complex and not well understood. These drugs stimulate peroxisome proliferator-activated receptors (PPARα). Activation of PPARα leads to an increase in lipoprotein lipase activity and a reduction in the production of apoprotein CIII (an inhibitor of lipoprotein lipase), causing a decrease in total triglycerides and triglyceride-rich lipoprotein (VLDL). In addition, these drugs upregulate the synthesis of apolipoprotein A-I, the building block of HDL, and, therefore, cause an increase in HDL.

Members of the Drug Class

In this section: Gemfibrozil, fenofibrate
Others: None

Gemfibrozil

Brand Name
Lopid

Generic Name
Gemfibrozil

Rx Only

Dosage Form
Tablet

Usage
Treatment of hypertriglyceridemia in Fredrickson types IV and V hyperlipidemia for patients who are at greater risk for pancreatitis and who have not responded to dietary intervention; to reduce the risk of coronary heart disease (CHD) development in Fredrickson type IIb patients without a history or symptoms of existing CHD who have not responded to dietary and other interventions (including pharmacologic treatment) and who have decreased HDL, increased LDL, and increased triglycerides

Pregnancy Category C

Dosing
- 600 mg twice daily 30 minutes before the morning and evening meals
- Renal dosage adjustment: Use caution in cases of mild to moderate renal impairment. Deterioration of renal function has been reported in patients with baseline serum creatinine > 2 mg/dl.

Adverse Reactions: Most Common
Dyspepsia, GI-related side effects, such as nausea, vomiting, diarrhea, constipation

Adverse Reactions: Rare/Severe/Important
Myalgias and more serious muscle-related adverse drug reactions, such as myopathy and rhabdomyolysis (risk is increased when gemfibrozil is combined with a statin), hepatotoxicity, cholelithiasis, gallstones

Major Drug Interactions
Gemfibrozil's Effect on Other Drugs
- Warfarin: Increases INR; an empiric reduction in warfarin dosage may be considered to minimize bleeding risk
- HMG-CoA reductase inhibitors: Increases the risk of myopathy and rhabdomyolysis. The risk is greater with gemfibrozil than fenofibrate; thus, fenofibrate is preferred for combination treatment with a statin.
- Repaglinide: Increases hypoglycemic effects. Use with caution in combination.

Contraindications
Hepatic or severe renal dysfunction; primary biliary cirrhosis; preexisting gallbladder disease

Essential Monitoring Parameters
- LFT elevations have been observed; however, these are reversible when gemfibrozil is discontinued. Therefore, periodic LFTs are recommended, and gemfibrozil therapy should be terminated if abnormalities persist.
- Worsening renal insufficiency upon the addition of gemfibrozil therapy has been reported in individuals with baseline plasma creatinine > 2 mg/dl. In such patients, the use of alternative therapy should be weighed against the risks and benefits of a lower dose of gemfibrozil.

Counseling Points
- Take 30 minutes before meals
- Avoid alcohol
- Report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever
- Use in conjunction with diet and exercise for optimal therapeutic effect

Key Points
- When combination therapy with a statin and a fibrate is required, fenofibrate may be preferred. The gemfibrozil–statin combination has an increased risk of myalgias, although rarely leading to myopathy and rhabdomyolysis.
- Gemfibrozil can individually increase the INR, and a patient's warfarin dose may be empirically reduced to avoid elevated bleeding risk

Fenofibrate

Brand Names
Antara, Fenoglide, Lipofen, Lofibra, TriCor, Triglide

Generic Name
Fenofibrate

Rx Only

Dosage Forms
Capsule, tablet

Usage
Adjunct to dietary therapy for the treatment of adults with elevations of serum triglyceride levels (types IV and V hyperlipidemia); adjunct to dietary therapy for the reduction of LDL, total cholesterol, TGs, and apolipoprotein B and to increase HDL in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson types IIa and IIb)

Limitations of Use
Fenofibrate at a dose equivalent to 145 mg of TriCor was not shown to reduce coronary heart disease morbidity and mortality in a large, randomized, controlled trial of patients with type 2 diabetes mellitus

Pregnancy Category C

Dosing

- Many different formulations are available; thus, doses can range from 50–200 mg daily
- Renal dosage adjustment: Use in severe renal impairment (including patients on dialysis) is contraindicated (see product labeling)

Adverse Reactions: Most Common

Dyspepsia, GI-related side effects, such as nausea, vomiting, diarrhea, constipation

Adverse Reactions: Rare/Severe/Important

Myalgias and more serious muscle-related adverse drug reactions, such as myopathy and rhabdomyolysis (risk is increased when fenofibrate is combined with a statin), hepatotoxicity, cholelithiasis, gallstones

Major Drug Interactions

Fenofibrate's Effect on Other Drugs

- Bile acid sequestrants: Potential pharmacokinetic interaction due to decreased absorption of fenofibrate. Fenofibrate should be administered 1 hour before or 4 to 6 hours after a bile acid sequestrant.
- Cyclosporine: Increases risk of cyclosporine-induced nephrotoxicity (i.e., deterioration in renal function). Use with caution.
- Warfarin: Increases INR; an empiric reduction in warfarin dosage may be considered to minimize bleeding risk
- HMG-CoA reductase inhibitors: Increases risk of adverse musculoskeletal effects (i.e., increased creatine kinase, myoglobinuria, rhabdomyolysis). Avoid concomitant use unless potential benefit outweighs risk.

Contraindications

Active liver disease, including primary biliary cirrhosis and unexplained, persistent liver function abnormality; severe renal impairment or end-stage renal disease (ESRD), including those receiving dialysis; preexisting gallbladder disease

Essential Monitoring Parameters

- Monitor LFTs regularly and discontinue therapy if LFTs remain greater than three times normal limits
- Monitor renal function in patients with renal impairment or in those at increased risk for developing renal impairment. Elevation in serum creatinine returns to baseline following discontinuation of fenofibrate. The clinical significance of these observations is unknown.

Counseling Points

- Report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever
- Use in conjunction with diet and exercise for therapeutic effects

Key Points

- Fenofibrate should be avoided in patients with severe kidney disease
- Fenofibrate can increase a patient's INR; the warfarin dose may be empirically reduced to avoid elevated bleeding risk

HMG-COA REDUCTASE INHIBITORS, STATINS

Introduction

Statins are considered first-line treatment for patients with dyslipidemia, in most patients with atherosclerotic cardiovascular disease (ASCVD), and in patients at risk of developing ASCVD. In 2013, the American College of Cardiology and American Heart Association (ACC/AHA) published a new Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. The 2013 ACC/AHA cholesterol guideline panel found that the vast majority of evidence indicating efficacy and safety of low-density lipoprotein (LDL) cholesterol lowering for risk reduction came from trials of statin drugs. In numerous clinical trials across many patient populations, statins have shown significant reduction in morbidity and mortality. Significant toxicities include myalgias that rarely lead to rhabdomyolysis. In February 2012, the FDA approved important safety label changes for statins. The changes included the removal of the guideline regarding routine monitoring of liver enzymes and the addition of information about the potential for generally nonserious and reversible cognitive side effects and reports of increased blood glucose and glycosylated hemoglobin (HbAlc) levels. Statins are contraindicated in patients with active liver disease. Because they are pregnancy category X drugs, they should not be used by women who are pregnant or breastfeeding.

Mechanism of Action for the Drug Class

HMG-CoA reductase inhibitors competitively inhibit hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase to mevalonate, which is the rate-limiting step in cholesterol biosynthesis. In addition, low-density lipoprotein cholesterol receptors are upregulated, enhancing the catabolic rate of LDL and reducing the plasma pool of LDL. The combination of these pharmacologic effects makes statins

highly effective LDL-lowering agents. To a lesser extent, they may also increase high-density lipoprotein (HDL) cholesterol and decrease triglycerides (TGs).

Members of the Drug Class

In this section: Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin
Other: Pitavastatin

Generic and Brand Names for the Drug Class

Atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor) lovastatin ER (Altoprev), pravastatin (Pravachol), simvastatin (Zocor), rosuvastatin (Crestor)

Rx Only for the Drug Class

Dosage Form for the Drug Class

Tablet

Usage for the Drug Class

- *Adjunct to diet and exercise, commonly referred to as therapeutic lifestyle changes (TLCs), for the treatment of various dyslipidemia disorders in patients with no evidence of cardiovascular disease (primary prevention) and in patients with documented coronary artery disease (secondary prevention)*
- Various dyslipidemias are described using the Fredrickson-Levy-Lees classification of hyperlipoproteinemia. Using this classification system, statins are primarily indicated for treatment of mixed dyslipidemia known as Fredrickson types IIa and IIb.
- Adjunct for treatment of hypertriglyceridemia (Fredrickson type IV hyperlipidemia) and primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia)

Pregnancy Category X for the Drug Class

Dosing for the Drug Class

- Statins should be used in combination with therapeutic lifestyle changes (TLCs). The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults made a significant departure from the previous guidelines. The use of fixed doses of cholesterol-lowering drugs to reduce ASCVD risk is the only approach that has been evaluated in multiple RCTs. The 2013 ACC/AHA guidelines focus on ASCVD risk reduction in four statin benefit groups and based on the risk group high-intensity and moderate-intensity statin therapy is recommended. **Tables 10-1** and **10-2** provide guidelines for statin dosing.
- Dosage adjustment:
  - Based on risk group (need to lower intensity if patient has dose limitation based on drug-drug interaction, intolerance, age, or comorbid conditions)

TABLE 10-1 Four Statin Benefit Groups and Major Recommendations from the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Four Statin Benefit Group			
Individuals with clinical ASCVD which includes acute coronary syndrome, myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin (Secondary Prevention)	Individuals with primary elevations of LDL ≥ 190 mg/dl (Primary Prevention)	Individuals 40 to 75 years of age with diabetes with LDL 70–189 mg/dl (Primary Prevention)	Individuals without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL 70–189 mg/dl and an estimated 10-year ASCVD risk of 7.5% or higher (Primary Prevention)
Major Recommendations			
High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤ 75 years of age who have *clinical ASCVD*, unless contraindicated. For patients age > 75 years, recommend moderate-intensity statin therapy.	Use high-intensity statin therapy unless contraindicated. Consider combining statin and non-statin therapy to further reduce LDL.	Calculate 10-yr risk of atherosclerotic CVD. If risk < 7.5%, moderate intensity statin therapy. If risk ≥ 7.5%, high-intensity statin therapy.	Calculate 10-yr risk of atherosclerotic CVD. If risk ≥ 7.5%, moderate-to high-intensity statin therapy. If ≥ 5% and < 7%, consider moderate-intensity statin. Before initiation of statin therapy for primary prevention, it is reasonable for clinicians and patients to engage in a discussion that considers the potential for ASCVD risk-reduction benefits and for adverse effects and drug–drug interactions, as well as patient preferences for treatment.

TABLE 10-2 High-, Moderate-, and Low-Intensity Statin Therapy (Adapted from 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults)

Low-Intensity	*Simvastatin 10* mg **Pravastatin 10–20** mg **Lovastatin 20** mg *Fluvastatin 20–40* mg *Pitavastatin 1* mg	Lowers LDL on average, by < 30%
Moderate-Intensity	**Atorvastatin 10**–*20* mg **Rosuvastatin** *5*–**10** mg **Simvastatin 20–40** mg **Pravastatin 40**–*80* mg **Lovastatin 40** mg *Fluvastatin XL 80* mg *Pitavastatin 2–4* mg	Lowers LDL on average, by ~ 30% ≤ 50%
High-Intensity	**Atorvastatin 40**[a]**–80** mg **Rosuvastatin 20**–*40* mg	Lowers LDL on average, by ~ ≥ 50%

Specific statins and doses that were evaluated in RCTs are noted in **bold**. Statins and doses that are approved by the FDA but were not tested in the RCTs are listed in *italics*.
[a]This dose was studied in one RCT only.
Republished with permission of Elsevier, from 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents, © 2016; permission conveyed through Copyright Clearance Center, Inc.

  - The use of 80 mg of simvastatin should be restricted to patients who have been receiving long-term therapy (e.g., ≥ 12 months) at this dosage without evidence of muscle toxicity
  - For less-than-anticipated therapeutic response (i.e., ≥ 50% decrease in LDL for high-intensity statin):
    - Reinforce improved adherence to lifestyle and drug therapy
    - Evaluate for secondary causes of hypercholesterolemia, if indicated
    - Increase statin intensity or if patient is receiving maximally tolerated statin intensity, consider addition of nonstatin therapy shown in RCT to reduce ASCVD events in selected high-risk persons. High-risk people include those with clinical ASCVD; those with an untreated LDL–C level 190 mg/dl, suggesting genetic hypercholesterolemia; or those aged 40 to 75 years with diabetes.
  - Decreasing the statin dose may be considered when two consecutive values of LDL–C levels are < 40 mg/dl.
- Renal dosage adjustment:
  - Atorvastatin: No adjustment is necessary
  - Fluvastatin: Use with caution in cases of severe renal impairment (doses > 40 mg daily have not been studied)
  - Pravastatin: Initial dose is 10 mg daily in patients with significant impairment
  - Lovastatin: If CrCl < 30 ml/min, then use with caution and carefully consider doses > 20 mg/day
  - Simvastatin: If CrCl < 30 ml/min, then initial dose is 5 mg daily with close monitoring
  - Rosuvastatin: In patients with CrCl < 30 ml/min who are not undergoing hemodialysis, initiate dosage of 5 mg once daily, not to exceed 10 mg once daily
- Hepatic dosage adjustment: All statins are contraindicated in active liver disease

Pharmacokinetic/Pharmacodynamic Properties

- The ability of a statin to lower LDL is very important in the treatment of dyslipidemia. Rosuvastatin and atorvastatin have the greatest ability to lower LDL (by approximately 60%), followed by simvastatin, lovastatin, pravastatin, and fluvastatin.
- The pharmacokinetic property of a particular statin plays an important role in the choice of statin for an individual patient. Increased bioavailability, decreased protein binding, long half-life, lipophilicity, and metabolism are all important characteristics that may influence the risk of developing statin-induced myopathies. Of all the properties just listed, metabolism is considered to be the most important due to the potential for drug interactions.
- Atorvastatin, lovastatin, and simvastatin are metabolized by the CYP3A4 system
- Fluvastatin is metabolized by the CYP2C9 system
- Rosuvastatin is metabolized by the CYP2C9 system to a limited extent
- Pravastatin is not metabolized by the CYP system; instead, it is metabolized by hydroxylation, oxidation, and conjugation

Adverse Reactions for the Drug Class: Most Common

- GI upset, myalgias (dose-related)

Adverse Reactions for the Drug Class: Rare/Severe/Important

- Myopathy (dose-related), rhabdomyolysis (dose-related)
- Hepatotoxicity (dose-related): Irreversible liver damage resulting from statins is exceptionally rare and is likely idiosyncratic in nature. No data exist that show that routine periodic monitoring of liver biochemistries is effective in identifying the very rare individual who may develop significant liver injury from ongoing statin therapy. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occur during treatment, therapy should be interrupted. If an alternate etiology is not found, the statin should not be restarted.
- Cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use has been rarely reported in the postmarketing period. These cognitive issues have been reported for all statins. The reports are generally nonserious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).
- A small increase in glycosylated hemoglobin (HbAlc) and fasting serum glucose levels (dose-related) have been reported with statin use; however, the benefits of statin therapy far outweigh the risk of dysglycemia

Major Drug Interactions for the Drug Class

- Enhanced toxicity with drugs that inhibit isoenzyme CYP3A4 and statins that are substrates of CYP3A4 (lovastatin, simvastatin, and atorvastatin). Dose limitations exist for certain inhibitors (e.g., simvastatin doses should be limited to 20 mg/day with amiodarone, amlodipine, ranolazine, and limited to 10 mg/day with verapamil and diltiazem; lovastatin doses should be limited to 40 mg/day with amiodarone and limited to 20 mg/day with verapamil and diltiazem). With strong CYP3A4 inhibitors, including itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, nefazodone, gemfibrozil, cyclosporine, human immunodeficiency virus (HIV) protease inhibitors, cobicistat-containing products, and the hepatitis C virus (HCV) protease inhibitors boceprevir and telaprevir, the use of lovastatin and simvastatin is contraindicated and/or should be avoided. Atorvastatin up to 20 mg/day can be used with clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir) because the extent of interaction between atorvastatin and CYP3A4 inhibitors is less than that with lovastatin and simvastatin.
- Rosuvastatin exposure can be increased via unknown mechanisms with protease inhibitors in combination with ritonavir; therefore, the dose of rosuvastatin in these combinations should be limited to 10 mg/day
- Statins are substrates for P-glycoprotein; therefore, drugs that inhibit P-glycoprotein (e.g., cyclosporine) may increase statin levels (e.g., in patients receiving cyclosporine limit rosuvastatin dose to 5 mg/day).
- Fibric acid derivatives increase the risk for myopathy/rhabdomyolysis due to additive effects of both drugs. Gemfibrozil can reduce the elimination of a statin by inhibiting glucuronidation, an elimination pathway of all statins except fluvastatin. Therefore, the use of fenofibrate, when combination therapy with a statin is required, may be a better choice. Dose limitation or avoidance of use is recommended when gemfibrozil is used in combination with a statin (e.g., limit rosuvastatin dose to 10 mg/day with gemfibrozil).

Contraindications

Active liver disease; unexplained persistent elevations of serum transaminases; pregnancy and lactation

Essential Monitoring Parameters for the Drug Class

Before starting therapy, check the patient's fasting lipid profile and check baseline liver function tests (LFTs) and repeat as clinically indicated. Baseline creatine phosphokinase (CPK) in high-risk patients may be checked. If the patient has symptoms of myalgia, check CPK.

Counseling Points for the Drug Class

- Report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever
- It is best to take statins with a short half-life, such as lovastatin, simvastatin, pravastatin, and fluvastatin, in the evening because of a greater lipid-lowering effect. Hepatic cholesterol production increases overnight.
- Take lovastatin with an evening meal because fat facilitates absorption
- Atorvastatin and rosuvastatin may be taken any time during the day without regard to meals because of their longer half-lives and more potent LDL cholesterol-lowering ability
- Avoid drinking grapefruit juice with statins metabolized by the CYP3A4 system

Key Points for the Drug Class

- Statins are first-line drugs of choice for prevention of cardiovascular disease
- When the combination therapy of a statin and fibrate is necessary, fenofibrate may be a better choice due to an increased risk of myopathy with gemfibrozil and a statin
- Be vigilant about dose limitation and avoidance of statins with concomitant use of inhibitors of the CYP3A4 system

NIACIN

Introduction

Niacin is a water-soluble B vitamin that is important for DNA repair and energy metabolism. When used in high doses of 1–2 g per day, niacin is an antilipemic agent. Because it is considered a vitamin, niacin is available as an OTC dietary supplement as well as by prescription. Niacin is available in three main dosage forms: immediate-release, slow/timed-release, and extended-release capsules, or tablets. The differences in formulations relate to flushing and hepatotoxicity risk. Niacin is the best-known agent to raise HDL. Niacin should not be used in patients with active liver disease or unexplained transaminase elevations. A large study, Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE), found there is no evidence of clinically significant benefit for the addition of niacin to statins and there is significant risk with combination therapy. Based on these findings, on April 18th, 2016, the FDA announced retraction of prior approvals related to coadministration of statins with niacin extended release (ER).

Mechanism of Action for the Drug Class

The exact mechanism of action is not fully understood. The process may involve inhibiting mobilization of free fatty acids from peripheral adipose tissue to the liver, resulting in decreased hepatic production of VLDL, ultimately decreasing LDL production. Niacin reduces the amount of apolipoprotein A-I extracted and catabolized from HDL during hepatic uptake, resulting in increased HDL.

Members of the Drug Class

In this section: Niacin
Others: None

◉ Niacin

Brand Names

Slo-Niacin, Niacor (IR), Niaspan ER (Rx), Niacin-Time

Generic Name

Niacin

Rx and OTC

Dosage Forms

Tablet, capsule

Usage

Mono- or adjunctive treatment of dyslipidemias (types IIa and IIb or primary hypercholesterolemia) to lower the risk of recurrent myocardial infarction (MI) and/or slow progression of coronary artery disease; *combination therapy with other antidyslipidemic agents when additional TG-lowering or HDL-increasing effects are desired; treatment of hypertriglyceridemia in patients at risk of pancreatitis*; treatment of pellagra (niacin deficiency); limitation of use: Addition of niacin ER did not reduce cardiovascular morbidity or mortality among patients treated with simvastatin in a large, randomized, controlled trial

Pregnancy Category C

Dosing

- Hyperlipidemia:
  - Immediate-release: 1.5–6 g daily in 3 divided doses with or after meals using an upward dosage titration schedule
  - Extended-release: Initial dose is 500 mg once daily at bedtime. Increase dosage by no more than 500 mg at 4-week intervals until desired effect is observed or maximum daily dosage of 2 g is reached.
- Pellagra:
  - 50–100 mg 3 to 4 times daily
  - Maximum: 500 mg daily

Adverse Reactions: Most Common

Flushing (prostaglandin-mediated) is most common with immediate-release products and least common with long-acting products; hyperglycemia, hyperuricemia, upper GI distress

Adverse Reactions: Rare/Severe/Important

Rise in serum transaminase values are seen with all niacin formulations, but the worst cases have been reported with slow-release niacin, and there is often a dose-related side effect when doses > 2000 mg/day are administered. Slow-release products should not be recommended due to increased hepatotoxicity risk. Immediate-release products have the least hepatotoxicity; however, they must be dosed three times daily and can cause significant flushing. Most experts prefer Niaspan (extended-release niacin) because it causes less flushing than immediate-release niacin, is dosed once daily, and is associated with less liver toxicity than sustained-release, controlled-release, or timed-release niacin (e.g., Slo-Niacin).

Major Drug Interactions

Drugs Affecting Niacin

Bile acid sequestrants: May decrease levels (give niacin 1 hour before or 4 to 6 hours after giving bile acid sequestrant)

Contraindications

Active hepatic disease or significant or unexplained persistent elevations in hepatic transaminases; active peptic ulcer; arterial hemorrhage

Essential Monitoring Parameters

Glucose levels should be closely monitored in diabetic or potentially diabetic patients, particularly during the first few months of use or dose adjustment. Liver function tests should be taken at baseline, every 6 to 12 weeks for the first year, and then periodically thereafter.

Counseling Point

Adherence may be compromised due to the adverse effects of flushing. Proper counseling reduces the incidence of flushing. The flushing occurs because of the release of prostaglandin D_2 from the skin. Taking aspirin or ibuprofen 30 minutes before therapy helps diminish this side effect. Patients should be advised to take niacin on a full stomach and that flushing may be worsened by hot, spicy food; hot beverages; hot baths; and hot showers.

Key Points

- Niacin is the best-known agent to raise HDL. The side effect of flushing may diminish adherence. Patients should be properly counseled on avoiding this side effect.
- The different formulations of niacin relate to the risk of hepatotoxicity and flushing. Products that claim to be "flush-free" or "no flush" are available OTC; however, these products fail to release free niacin, making them ineffective antilipemic agents.

OMEGA-3 FATTY ACIDS

Introduction

Omega-3 fatty acids are polyunsaturated fatty acids derived from marine and plant sources. Omega-3 fatty acids can decrease triglycerides by 50%, although in patients with very high triglycerides (> 500 mg/dl), there is an increase in LDL. Omega-3 fatty acids are available as dietary supplements; however, the amounts of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are lower compared with the only prescription product, Lovaza. Lovaza is the purest form of omega-3 fatty acids and contains 85% of EPA and DHA in a 1000-mg capsule. Approved in 2012, ethyl eicosapentaenoic acid (EPA) (Vascepa®) is the newest addition to triglyceride management. One advantage of the EPA-only formulation is that it does not elevate LDL, unlike EPA/DHA combinations. Vascepa contains ≥ 96% EPA and does not contain docosahexaenoic acid (DHA).

Mechanism of Action for the Drug Class

The mechanism of action has not been completely defined. Possible mechanisms include inhibition of acyl CoA:1,2-diacyl-glycerol acyltransferase, increased hepatic beta-oxidation, a reduction in the hepatic synthesis of triglycerides, or an increase in plasma lipoprotein lipase activity.

Members of the Drug Class

In this section: Omega-3 fatty acids
Others: None

◉ Omega-3 Fatty Acids

Brand Name

Lovaza

Generic Name

Omega-3 fatty acids

Rx (Lovaza, Vascepa) and OTC

Dosage Form

Capsule

Usage

Adjunct to diet therapy in the treatment of hypertriglyceridemia (≥ 500 mg/dl), prophylaxis to prevent a myocardial infarction (unlabeled use), treatment of immunoglobulin (Ig)A nephropathy (unlabeled use)

Pregnancy Category C

Dosing

- Lovaza:
  - Hypertriglyceridemia/treatment of IgA nephropathy: 4 g daily as a single dose or in 2 divided doses
  - Prophylaxis to prevent a myocardial infarction: 1 g daily
- Vascepa:
  - Hypertriglyceridemia: 2 g twice daily with meals

Adverse Reactions: Most Common

Generally well tolerated. The most common side effect is a "fishy" smelling burp called eructation, fishy aftertaste, and GI upset/nausea. Refrigeration of the capsules may help minimize these side effects.

Adverse Reactions: Rare/Severe/Important

Increase in bleeding time, although this does not appear to exceed the normal range of bleeding time

Major Drug Interactions

Omega-3 Fatty Acids' Effect on Other Drugs

Antiplatelet agents and warfarin: May increase levels/effects. More frequent monitoring may be necessary in patients taking warfarin.

Essential Monitoring Parameters

In patients with hepatic impairment, monitor ALT and AST levels periodically during therapy. Omega-3 fatty acids (especially EPA/DHA combination products) may increase levels of LDL. Monitor LDL levels periodically during therapy.

Counseling Point

OTC products differ in their EPA/DHA content. It is important to note the total amount of omega-3 fatty acids contained in each capsule rather than the amount of fish oil concentrate. Some products may require consumption of up to 11 capsules to obtain the same amount of omega-3 fatty acid content that is obtained from 4 capsules of Lovaza.

Key Point

Omega-3 fatty acids are increasingly being used for prevention of myocardial infarction at doses of 1 g daily. Higher doses of 2–4 g daily are used to lower TGs.

PROPROTEIN CONVERTASE SUBTILISIN KEXIN TYPE 9 (PCSK9) INHIBITORS

Introduction

PCSK9 is an important enzyme (serine protease) encoded by the PCSK9 gene for LDL receptor function. Gene mutations in PCSK9 can result in changes in PCSK9 function. For example, patients with loss of PCSK9 function have low plasma LDL concentrations, which is associated with lower CVD risk. Therefore, inhibition of PCSK9 prevents the binding of the enzyme to the LDL receptors and subsequently decreasing LDL receptor degradation. This results in lower LDL concentrations from allowing more LDL receptors to be available at the surface of the hepatocyte to clear LDL from the blood stream. The FDA approved two fully humanized monoclonal antibodies to PCSK9, alirocumab and evolocumab. These agents dramatically reduce LDL levels (an additional 45% to 64%) over and above statin therapy, with favorable short-term outcomes data up to 18 months. Long-term cardiovascular outcomes trials are ongoing for both alirocumab and evolocumab. These agents are administered subcutaneously and are considered specialty medications with estimated cost of $14,000 annually.

Mechanism of Action for the Drug Class

Fully humanized monoclonal antibody that inhibits the binding of Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) to low-density lipoprotein receptors (LDLRs) on hepatocytes, thus reducing degradation of the LDLR. Increased LDLRs are then available to clear LDL from circulation and lower LDL levels.

Members of the Drug Class

In this section: alirocumab and evolocumab
Others: none

⦿ Alirocumab

Brand Names

Praluent

Generic Name

Alirocumab

Rx Only

Dosage Form

Pre-filled pen or syringe

Usage

As adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL.
Limitations of Use: The effect of Praluent on cardiovascular morbidity and mortality has not been determined.

Pregnancy

Risk Summary: There are no available data on use of Praluent in pregnant women to inform a drug-associated risk. Animal data can be found in the package insert. Alirocumab can cross the placental barrier more so in the second and third trimester.

Dosing

Hyperlipidemia: SubQ: 75 mg once every 2 weeks; may increase to 150 mg once every 2 weeks if an adequate response is not achieved within 4 to 8 weeks
Renal and hepatic impairment: no dosage adjustment necessary

Adverse Reactions: Most Common

Most commonly occurring adverse reactions (≥ 5% of patients) are nasopharyngitis, injection-site reactions, and influenza

Adverse Reactions: Rare/Severe/Important

Hypersensitivity reaction, antibody development, increases self-reported cognitive adverse effect (confusion, memory impairment), decreased LDL (≤ 25 mg/dl)

Major Drug Interactions

No clinically significant drug-drug interactions have been identified.

Contraindications

Documentation of allergenic cross-reactivity for PCSK9 inhibitors is limited. However, because of similarities in

chemical structure and/or pharmacologic actions, the possibility of cross-sensitivity cannot be ruled out with certainty.

Essential Monitoring Parameters

LDL cholesterol (LDL-C; within 4 to 8 weeks of initiation or dose titrations). Monitor for hypersensitivity reactions.

Counseling Points

- Discontinue and seek prompt medical attention if any signs or symptoms of serious allergic reaction
- Proper guidance to patients and caregivers on aseptic subcutaneous injection technique and how to use the prefilled pen or prefilled syringe correctly. Inform patients that it may take up to 20 seconds to inject.
- Prefilled pen or syringe should be allowed to warm to room temperature for 30 to 40 minutes prior to use. Time out of refrigeration should not exceed 24 hours.
- Prefilled pen or syringe must not be reused and patients and caregivers are to be instructed in the technique of proper pen and syringe disposal in a puncture-resistant container. Do not recycle the container.

Key Point

PCSK9 inhibitors provide substantial LDL reduction in addition to statin therapy. Robust cardiovascular outcomes trials are yet to be completed. They are cost prohibitive and require a burdensome prior authorization process and are considered specialty drugs. They require SubQ administration and proper counselling is required for storage and administration.

◉ Evolocumab

Brand Names

Repatha

Generic Name

Evolocumab

Rx Only

Dosage Form

Single-use prefilled syringe or SureClick autoinjector
Single-use Pushtronex system (on-body infusor with prefilled cartridge)

Usage

As adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL. Other LDL-lowering therapies (e.g. statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia who require additional lowering of LDL. Limitations of use: The effect of Repatha on cardiovascular morbidity and mortality has not been determined.

Pregnancy

Risk summary: There are no available data on use of Repatha in pregnant women to inform a drug-associated risk. Animal data can be found in the package insert. Evolocumab can cross the placental barrier more so in the second and third trimester.

Dosing

- Hyperlipidemia, primary or heterozygous familial hypercholesterolemia: SubQ: 140 mg every 2 weeks or 420 mg once monthly
- Homozygous familial hypercholesterolemia: SubQ: 420 mg once monthly
- Renal and hepatic impairment: no dosage adjustment necessary

Adverse Reactions: Most Common

Most commonly occurring adverse reactions (≥ 5% of patients) are nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection-site reactions

Adverse Reactions: Rare/Severe/Important

- Hypersensitivity reactions (e.g., rash, urticaria) have been reported, some requiring discontinuation. Discontinue treatment and initiate supportive treatment in patients who develop signs/symptoms of serious allergic reaction; monitor until symptoms resolve.
- Antibody development
- Increases self-reported cognitive adverse effect (confusion, memory impairment)
- Decreased LDL (≤ 25 mg/dl)

Major Drug Interactions

No clinically significant drug-drug interactions have been identified.

Contraindications

Documentation of allergenic cross-reactivity for PCSK9 inhibitors is limited. However, because of similarities in chemical structure and/or pharmacologic actions, the possibility of cross-sensitivity cannot be ruled out with certainty.

Essential Monitoring Parameters

Lipid profile; in patients with homozygous familial hypercholesterolemia, measure LDL levels 4 to 8 weeks after initiation (response to evolocumab will depend on degree of LDL-receptor function); signs/symptoms of hypersensitivity reactions

Counseling Points

- Proper guidance to patients and caregivers on proper subcutaneous administration technique, including aseptic technique and how to use the single-use prefilled autoinjector, single-use prefilled syringe, or single-use, on-body infusor with prefilled cartridge correctly
- Inform patient that it may take 15 seconds to administer Repatha using the single-use prefilled autoinjector or single-use prefilled syringe and about 9 minutes to administer Repatha using the single-use, on-body infusor with prefilled cartridge

- Store refrigerated in the original carton. Alternatively, Repatha can be kept at room temperature in the original carton for 30 days. Discard after 30 days, if not used.
- Needle cover of the glass, single-use prefilled syringe and the single-use prefilled autoinjector contain dry natural rubber, which may cause allergic reactions in individuals sensitive to latex. The body infusor with prefilled cartridge is not made with natural rubber latex.

Key Point

PCSK9 inhibitors provide substantial LDL reduction in addition to statin therapy. Robust cardiovascular outcomes trials are yet to be completed. They are cost prohibitive and require a burdensome prior authorization process and are considered specialty drugs. They require SubQ administration and proper counseling is required for storage and administration.

REVIEW QUESTIONS

1. The MOA of PCSK9 inhibitor is
   - a. Monoclonal antibody that inhibits the binding of PCSK9 to low-density lipoprotein receptors (LDLRs) on hepatocytes, thus reducing degradation of the LDLR
   - b. PCSK9 inhibitor binds to bile acids in the gut, which interrupts recycling through enterohepatic recirculation
   - c. Inhibition of acyl CoA:1,2-diacyl-glycerol acyltransferase, increased hepatic beta-oxidation, a reduction in the hepatic synthesis of triglycerides, or an increase in plasma lipoprotein lipase activity
   - d. Inhibition of cholesterol absorption at the brush border of the small intestine via the sterol transporter Niemann-Pick C1-Like1, leading to decreased delivery of cholesterol to the liver, reduction of hepatic cholesterol stores, and increased clearance of cholesterol from the blood

2. The brand name of alirocumab is
   - a. Vascepa
   - b. Praluent
   - c. Repatha
   - d. Lipitor

3. Which of the following is true of PCSK9 inhibitors?
   - a. They are administered orally
   - b. They provide a modest LDL reduction in addition to statin therapy
   - c. They are cost prohibitive and require a burdensome prior authorization process
   - d. Numerous robust cardiovascular outcomes trials show a substantial decrease in CV morbidity and mortality

4. Which of the following is a side effect of PCSK9 inhibitor?
   - a. Antibody development
   - b. Increase in TG
   - c. Improvement in memory
   - d. Paradoxical increase in LDL

5. Which PCSK9 inhibitor is approved for treatment of homozygous and heterozygous familial hypercholesterolemia?
   - a. Praluent
   - b. Repatha
   - c. Praluent and Repatha
   - d. None of the above

6. PCSK9 inhibitors are administered via
   - a. Oral route
   - b. Intramuscular injection
   - c. Subcutaneous injection
   - d. Intravenous infusion

7. PCSK9 inhibitors dramatically reduce LDL levels (an additional 45% to 64%) over and above statin therapy.
   - a. True
   - b. False

8. The PCSK9 inhibitors—alirocumab or evolocumab—are a _____ monoclonal antibody that inhibits the binding of PCSK9 to low density lipoprotein receptors (LDLRs) on hepatocytes.
   - a. Humanized
   - b. Chimeric
   - c. Murine
   - d. Human

9. Which of the following is true about Vascepa?
   - a. It is an EPA-only formulation that does not elevate LDL
   - b. It does not cause "fishy" smelling burps called eructation or fishy aftertaste
   - c. For treatment of hypertriglyceridemia, it should be dosed 4 g twice daily before meals
   - d. It is exactly the same as Lovaza except that it is manufactured by a different company

10. Which of the following drug(s) is/are available OTC as dietary supplements? (select all that apply)
    a. Niacin
    b. Fish oils
    c. Ezetimibe
    d. Statins

11. On April 18th 2016, the FDA announced retraction of prior approvals related to coadministration of statins with
    a. Ezetimibe
    b. Cholestyramine
    c. Niacin ER
    d. Evolocumab

12. Based on the 2013 ACC/AHA lipid guidelines, which is the BEST patient to recommend a *high* intensity statin?
    a. 47-year-old male with past medical history of anterior wall myocardial infarction
    b. 80-year-old female with a history of CAD s/p non Q-wave MI
    c. 30-year-old with a history of smoking and high lifetime ASCVD risk score of 50% and no 10-year ASCVD risk score due to his young age of less than 40
    d. 55-year-old with a history of diabetes and 10 year ASCVD score of 5%

13. Based on the 2013 ACC/AHA guidelines, the following statins doses are classified as high intensity. (Select all that apply)
    a. Atorvastatin 80 mg daily
    b. Rosuvastatin 40 mg daily
    c. Simvastatin 20 mg QHS
    d. Lovastatin 40 mg QHS

14. Based on the 2013 ACC/AHA lipid guidelines, which is the BEST patient to recommend a *moderate* intensity statin?
    a. 47-year-old male with past medical history of anterior wall myocardial infarction
    b. 80-year-old female with a history of CAD s/p non Q-wave MI
    c. 30-year-old male with a family history of early cardiac disease, xanthoma, and LDL 200 mg/dl
    d. 55-year-old female with a history of diabetes and 10 year ASCVD score of 15%

15. Which of the following statin(s) is/are contraindicated in a patient with past medical history of HIV treated with cobicistat-containing products? (Select all that apply)
    a. Simvastatin
    b. Lovastatin
    c. Pravastatin
    d. Rosuvastatin

16. Which study found there is no evidence of clinically significant benefit for the addition of niacin to statins and that there is significant risk with the combination therapy?
    a. Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE)
    b. Action to Control Cardiovascular Risk in Diabetes (ACCORD)—lipids
    c. The Study of Heart and Renal Protection (SHARP)
    d. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)

17. Which of the following is/are indication(s) for use of bile acid sequestrants?
    a. Adjunct to diet in the management of primary hypercholesterolemia
    b. Pruritus associated with elevated levels of bile acids
    c. Diarrhea associated with excess fecal bile acids
    d. All of the above

18. Which of the following drugs can be used for binding toxicologic agents?
    a. Cholestyramine
    b. Fenofibrate
    c. Simvastatin
    d. Omega-3 fatty acids

19. Before starting therapy with HMG-CoA reductase inhibitors, which of the following laboratory tests should be checked?
    a. Liver function tests
    b. Complete blood count
    c. Lupus anticoagulant
    d. Electrocardiogram

20. Routine monitoring of liver function tests is recommended after initiating HMG-CoA reductase inhibitor therapy.
    a. True
    b. False

21. Routine monitoring of creatine phosphokinase is recommended after initiating HMG-CoA reductase inhibitor therapy.
    a. True
    b. False

22. Statins increase HbA1c/fasting glucose in a dose-dependent manner. Most data indicate that benefits of statins do outweigh the risk of developing diabetes.
    a. True
    b. False

23. Which of the following combinations has shown modest meaningful clinical outcome data for reduction in cardiovascular-related morbidity?

- **a.** Simvastatin plus fenofibrate
- **b.** Simvastatin plus niacin ER
- **c.** Simvastatin plus ezetimibe

24. In patients with severe kidney disease, the following drug should be avoided?

- **a.** Fenofibrate
- **b.** Atorvastatin
- **c.** Omega-3 fatty acids
- **d.** Cholestyramine

25. The dosage of simvastatin should be limited to _____ daily for patients who are concomitantly receiving treatment with verapamil.

- **a.** 10 mg
- **b.** 20 mg
- **c.** 30 mg
- **d.** 40 mg

26. Which of the following is/are brand names of fenofibrate?

- **a.** TriCor
- **b.** Triglide
- **c.** Antara
- **d.** All of the above

27. For prevention of cardiovascular disease, which class of drugs is considered first line?

- **a.** Fibrates
- **b.** Niacin
- **c.** Statins
- **d.** PCSK9 inhibitors

28. Cholelithiasis is a potential adverse event of the following drug:

- **a.** Gemfibrozil
- **b.** Lovastatin
- **c.** Niacin
- **d.** Colesevelam

29. Which of the following agents should be avoided in a patient with TG of 500 mg/dl?

- **a.** Cholestyramine
- **b.** Gemfibrozil
- **c.** Atorvastatin
- **d.** Niacin

30. A potential side effect of statin plus PCSK9 inhibitor therapy is decrease in LDL to less than 25 mg/dl.

- **a.** True
- **b.** False

CHAPTER 11

Miscellaneous Agents

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5-ALPHA REDUCTASE INHIBITORS

Introduction

The 5-alpha reductase inhibitors are agents that interfere with testosterone's stimulatory effect on the size of the prostate gland. They are used to reduce prostate size and alleviate urinary obstruction and the symptoms associated with benign prostatic hyperplasia (BPH), including urinary hesitancy, urgency, and nocturia. These actions may slow disease progression and decrease the risk of disease complications. The 5-alpha reductase inhibitors also slow the progression of male-pattern baldness.

Mechanism of Action for the Drug Class

These drugs competitively inhibit 5-alpha reductase in the prostate, liver, and skin, blocking the conversion of testosterone to dihydrotestosterone (DHT). DHT is an androgen that stimulates prostate growth and contributes to male-pattern baldness.

Members of the Drug Class

In this section: Finasteride, Dutasteride

◉ Finasteride

Brand Names
Propecia, Proscar

Generic Name
Finasteride

Rx Only

Dosage Form
Tablet

Usage
Treatment of moderate to severe BPH, treatment of male-pattern baldness in men

Pregnancy Category X

Dosing
- BPH: 5 mg daily
- Male-pattern baldness: 1 mg daily

Adverse Reactions: Most Common
Reduced libido, ejaculation disturbances, impotence

Adverse Reactions: Rare/Severe/Important
Testicular pain, gynecomastia, neoplasm of male breast, may increase risk of high-grade prostate cancer

Major Drug Interactions
No known significant drug interactions

Contraindications
Pregnancy, use in women of childbearing potential, children

Essential Monitoring Parameter
Finasteride predictably decreases the PSA level; establish a new baseline PSA 6 months post-initiation, then monitor periodically

Counseling Points
- Women of childbearing age should not touch or handle broken tablets due to risk of cutaneous absorption
- Results of therapy may take several months
- This medication can be taken with or without meals

◉ Dutasteride

Brand Names
Avodart

Generic Name
Dutasteride

Rx Only

Dosage Form
Capsule

Usage
Treatment of moderate to severe BPH

Pregnancy Category X

Dosing
0.5 mg daily

Adverse Reactions: Most Common
Impotence, reduced libido, ejaculation disturbance (all low incidence)

Adverse Reactions: Rare/Severe/Important
May increase risk of high-grade prostate cancer

Major Drug Interactions
Strong CYP3A4 inhibitors can increase dutasteride concentrations

Contraindications
Known or suspected pregnancy, use in women of childbearing potential, children

Essential Monitoring Parameter
Dutasteride predictably decreases the PSA level; establish a new baseline PSA > 3 months post-initiation, then monitor periodically

Counseling Points
- Women of childbearing age should not touch or handle capsules due to risk of cutaneous absorption
- Results of therapy may take several months
- This medication can be taken with or without meals

Key Points for the Class
- These drugs are pregnancy category X because they can cause abnormalities of the external genitalia of the male fetus. Females of childbearing age should not handle tablets or capsules.
- Typically dispensed in sealed container or unit-dose package to minimize handling
- A minimum of 3 to 6 months may be needed to determine effectiveness

ALPHA-1 ADRENERGIC BLOCKERS

Introduction
Alpha-1 adrenergic blockers are used in the treatment of hypertension but are currently used more often in the treatment of benign prostatic hyperplasia (BPH). Tamsulosin, due to its selectivity, is not indicated for the treatment of hypertension.

Mechanism of Action for the Drug Class
Alpha-1 adrenergic blockers cause vasodilation by selectively blocking postsynaptic alpha-1 adrenergic receptors, resulting in dilation of both peripheral arterioles and veins. They also relax smooth muscles in the prostate and bladder neck. Tamsulosin is selective for alpha-receptors in the prostate and does not have a therapeutic effect on blood pressure, although orthostatic hypotension is still possible, as with other members of this class.

Members of the Drug Class
In this section: Tamsulosin
Others: terazosin, alfuzosin, phenoxybenzamine, phentolamine, prazosin, silodosin

◉ Tamsulosin

Brand Name
Flomax

Generic Name
Tamsulosin

Rx Only

Dosage Form
Capsule

Usage
Treatment of BPH, symptomatic treatment of bladder outlet obstruction, facilitation of expulsion of ureteral stones

Pregnancy Category B

Dosing
- Initial dose: 0.4 mg daily
- Dosage adjustment: Can increase in 2 to 4 weeks to maximum of 0.8 mg daily

Adverse Reactions: Most Common
Dizziness, headache, orthostatic hypotension, syncope, flushing, ejaculation failure

Adverse Reactions: Rare/Severe/Important
Intraoperative floppy iris syndrome (in patients undergoing cataract surgery), priapism, symptoms of angina

Major Drug Interactions

Drugs Affecting Tamsulosin

Concomitant antihypertensive agents and phosphodiesterase-5 inhibitors: Additive hypotension. Strong CYP3A4 inhibitors increase tamsulosin's effects, strong CYP3A4 inducers can increase tamsulosin metabolism

Tamsulosin's Effect On Other Drugs

Antihypertensive agents: Additive hypotension

Counseling Points

- Take 30 minutes after the same meal each day
- Do not crush, chew, or open capsule
- May cause dizziness or drowsiness (take at night to avoid)
- May require 1 to 2 weeks of therapy before improvement of BPH symptoms

Key Points

- Because it is a selective alpha-agonist, it has minimal effects on blood pressure and is used only for the treatment of BPH
- Avoid concomitant use of phosphodiesterase-5 inhibitors (sildenafil, tadalafil, vardenafil)
- Tamsulosin is often used with a 5-alpha reductase inhibitor

ACNE PRODUCTS, RETINOIC ACID DERIVATIVES

Introduction

Topical retinoic acid derivatives are commonly used in the treatment of mild to moderate acne; however, the oral retinoic acid derivative isotretinoin is reserved for severe cases of acne that have been unresponsive to conventional therapies, including anti-infectives. Unlike other therapies, the beneficial effect of isotretinoin is prolonged beyond discontinuation of therapy. Isotretinoin requires special monitoring due to its side-effect profile.

Mechanism of Action for the Drug Class

Isotretinoin reduces sebaceous gland size and sebum production. Regulates cell proliferation and differentiation.

Members of the Drug Class

In this section: Isotretinoin
Others: Topical tretinoin

◉ Isotretinoin

Brand Names

Claravis, Absorica, Myorisan, Zenatane

Generic Name

Isotretinoin

Rx Only

Dosage Form

Capsule

Usage

Treatment of severe recalcitrant nodular acne that is unresponsive to conventional therapy, moderate acne

Pregnancy Category X

Dosing

Adults and children ≥ 12 years of age: 0.5–1 mg/kg/day in two divided doses given with meals for 15 to 20 weeks or until the total nodule count decreases by 70%, whichever occurs first; severe scarring may require 2 mg/kg/day
Moderate acne: 20 mg/day for 6 months

Adverse Reactions: Most Common

Cheilitis, conjunctivitis, hair thinning, elevated triglycerides, dry skin, photosensitivity, pruritus, xerostomia, arthralgia, backache, dry nasal mucosa, and epistaxis

Adverse Reactions: Rare/Severe/Important

Pancreatitis, neutropenia, hepatotoxicity, anaphylaxis, visual disturbances, hearing loss, aggressive behavior, depression, psychosis, skeletal hyperostosis, osteoporosis, pseudotumor cerebri

Major Drug Interactions

Drugs Affecting Isotretinoin

- Vitamin A derivatives and multivitamins containing vitamin A: Additive toxicity (i.e., dry skin and mucous membranes)
- Ethanol: Increases risk of elevated triglycerides

Isotretinoin's Effect on Other Drugs

- Tetracyclines: May increase the risk of pseudotumor cerebri
- Contraceptives: May decrease effectiveness of oral contraceptives

Essential Monitoring Parameters

Lipid panel with serum triglycerides, liver function tests, CBC, pregnancy tests

Contraindications

Patients who are pregnant or who may become pregnant, nursing women

Counseling Points

- Avoid pregnancy during treatment with isotretinoin
- Counsel men about the risks associated with impregnating a woman taking isotretinoin
- Take with meals; failing to take isotretinoin with food can significantly reduce drug absorption (except Absorica)
- The capsule should be swallowed whole with a full glass of water
- Exacerbations of acne can occur during first week of treatment
- Immediately report any of the following to your healthcare provider: Visual difficulties, abdominal pain, rectal bleeding, feelings of depression, and/or suicidal ideation
- Avoid prolonged sun exposure, use sunscreen, and wear protective clothing
- Manage cheilitis (dry mouth, cracked skin around lips, nose, and eyes) with lip balms, sugarless candy, saline nasal spray, and artificial tears

Key Points

- Last-line therapy for severe nodular acne
- Drug is pregnancy category X; it can cause craniofacial, cardiovascular, thymus, parathyroid gland, and CNS structure malformations in a developing fetus
- All patients (male and female), prescribers, wholesalers, and dispensing pharmacists must register and be active in the iPLEDGE risk management program designed to eliminate fetal exposure to isotretinoin
  - Female patients:
    - No woman should be pregnant or become pregnant when prescribed isotretinoin or for at least 1 month following isotretinoin treatment
    - Female patients must have two negative pregnancy tests before a prescription for isotretinoin is written. Additionally, they are required to have a pregnancy test each month during treatment.
    - Women must have selected and committed to use two forms of contraception for 1 month prior, during, and for 1 month after isotretinoin treatment
  - Male patients:
    - Male patients should be aware of the possibility of birth defects in an unborn child exposed to isotretinoin
- Women and men should not donate blood while taking isotretinoin
- No more than a 30-day supply of isotretinoin should be dispensed
- Prescriptions for isotretinoin can only be filled within 7 days of the date of the "qualification"
- No refills are permitted

ANTIMALARIALS, AMINOQUINOLINES

Introduction

Hydroxychloroquine is an antimalarial that is also used to treat rheumatoid arthritis (RA) and autoimmune conditions that are not related to malaria. It is important to be familiar with the side-effect profile of this medication to know how to minimize the adverse effects.

Mechanism of Action for the Drug Class

Although the exact mechanisms remain unclear, there are several proposed theories regarding the role of aminoquinolines in different diseases. Drugs in this class produce a lethal accumulation of cytotoxic heme within sensitive malarial parasites. Regarding RA and SLE, these agents increase the pH within intracellular vacuoles and interfere with the ability of macrophages and other antigen-presenting cells to process antigens. There is a resulting diminished presentation of antigens, which is required to stimulate CD4+ T cells. Ultimately, the immune response against autoantigenic peptides and the inflammatory process are downregulated. Additional immunomodulatory mechanisms include a reduction in proinflammatory cytokines via inhibition of the immune response on Toll-like receptors, blockage of ultraviolet light in cutaneous reactions. In SLE patients, this can result in improved control of cutaneous, musculoskeletal, cardiovascular, atherosclerotic, and thrombotic manifestations. In RA patients, hydroxychloroquine has demonstrated efficacy as a disease-modifying antirheumatic drug (DMARD), with the potential to improve glycemic control and lipid profiles.

Members of the Drug Class

In this section: Hydroxychloroquine
Others: Chloroquine, primaquine

◉ Hydroxychloroquine

Brand Name

Plaquenil

Generic Name

Hydroxychloroquine

Rx Only

Dosage Form

Tablet

Usage

Treatment of chronic discoid and systemic lupus erythematosus (SLE), treatment of RA, treatment of acute attacks and prophylaxis of malaria caused by Plasmodium vivax, Plasmodium malariae, Plasmodium ovale, and susceptible strains of Plasmodium falciparum, Q fever, porphyria cutanea tarda, polymorphous light eruption

Pregnancy Category D

Dosing

Hydroxychloroquine sulfate 200 mg is equivalent to 155 mg hydroxychloroquine base and 250 mg chloroquine phosphate. All doses listed below are expressed as hydroxychloroquine sulfate.

- Malaria:
  - Chemoprophylaxis:
    - Adults: 400 mg once weekly on the same day of each week, beginning 2 weeks before exposure and continuing for 4 weeks after leaving the endemic area. If suppressive therapy is not begun before the exposure, double the initial dose, and give in two doses, 6 hours apart and continue treatment for 8 weeks.
    - Weight-based dosing in adults and pediatric patients: 6.5 mg/kg, not to exceed 400 mg, once weekly on the same day of the week, beginning 2 weeks before exposure and continuing for 4 weeks after leaving the endemic area.
  - Treatment of uncomplicated malaria:
    - Adults: Initial dose of 800 mg followed by 400 mg at 6, 24, and 48 hours after the initial dose.
    - Weight-based dosage in adults and pediatric patients: 13 mg/kg, not to exceed 800 mg, followed by 6.5 mg/kg, not to exceed 400 mg at 6, 24, and 48 hours after the initial dose.
    - For radical cure of *P. vivax* and *P. malariae* infections, use concomitantly with an eight-aminoquinoline compound.
- Rheumatoid arthritis:
  - Initial adult dose: 400–600 mg daily, administered as a single daily dose or in two divided doses; increase dose gradually until optimum response level is reached
  - Maintenance dose: After 4 to 12 weeks, the dose may be reduced by half to a maintenance dose of 200–400 mg daily, administered as a single daily dose or in two divided doses
  - Maximum dose: 600 mg or 6.5 mg/kg per day, whichever is lower
- SLE:
  - Adult dose: 200–400 mg daily
  - Maximum dose: 400 mg or 5 mg/kg (using actual body weight) once daily
- Renal dosage adjustment: There are no dosage adjustments provided in manufacturer's labeling. Use with caution in patients with renal impairment.
- Hepatic dosage adjustment: There are no dosage adjustments provided in manufacturer's labeling. Use with caution in patients with hepatic impairment.

Adverse Reactions: Most Common

Skin pigmentation changes (blue/back), nausea, vomiting, diarrhea, myopathy, headache, dizziness, corneal changes, fatigue, urticaria

Adverse Reactions: Rare/Severe/Important

Stevens-Johnson syndrome, agranulocytosis, aplastic anemia, leukopenia, thrombocytopenia, irreversible retinopathy, loss of visual acuity, night blindness, blurred vision, neuromyopathy, cardiomyopathy and cardiac failure, extrapyramidal symptoms, hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency

Major Drug Interactions

Drug Affecting Hydroxychloroquine

- Dapsone: Additive risk of hemolytic reactions such as blood dyscrasias

Hydroxychloroquine's Effect on Other Drugs

- Cyclosporine: Increases serum concentrations
- Digoxin: Increases serum concentrations
- Insulin or antidiabetic drugs: Enhanced hypoglycemic effects
- Mefloquine: Lowers convulsive threshold, increasing risk of seizures and QT interval prolongation
- Metoprolol: Increases plasma levels
- Phenothiazine antipsychotics: Increases plasma levels

Contraindication

- Retinal or visual field changes attributable to 4-amino-quinoline derivatives or to any other etiology

Essential Monitoring Parameters

- Obtain ophthalmic examinations at baseline and annually after 5 years of use
- CBC at baseline and periodically thereafter
- Liver function tests
- Signs of cardiomyopathy or cardiac failure

Counseling Points

- Report any visual changes to a healthcare professional
- This medication may increase sensitivity to sunlight. Therefore, wear dark glasses and protective clothing, use sunblock, and avoid direct exposure to sunlight.
- GI side effects are short lived and typically managed by taking the medication with food or milk

Key Points

- This is not the preferred first-line agent in the treatment of RA and SLE and in the prevention and treatment of malaria
- Significant risk factors for irreversible retinal damage include daily doses of hydroxychloroquine 6.5 mg/kg of actual body weight, duration of use greater than 5 years, renal impairment, use of some concomitant drug products (such as tamoxifen), and concurrent macular disease
- Cardiomyopathy resulting in cardiac failure has been reported with high daily doses
- Use with caution in patients with G6PD deficiency because it can be associated with hemolysis
- Use with caution in patients with psoriasis, due to potential for exacerbation of symptoms or precipitation of a severe acute flare

ANALGESICS, OPIOID PARTIAL AGONISTS

Introduction

Buprenorphine/naloxone is used to treat opioid addiction. This combination formulation discourages parenteral misuse by producing withdrawal symptoms, if injected.

Mechanism of Action for the Drug Class

Buprenorphine is a mixed agonist–antagonist medication. It exhibits high-affinity binding to μ-opioid receptors, where it acts as partial agonist and is also a weak kappa receptor antagonist. It binds to the CNS opiate receptors, where it produces an analgesic effect. Naloxone is a μ-opioid receptor antagonist, which also competes and displaces opioids at the μ and kappa receptor sites in the CNS.

Members of the Drug Class

In this section: Buprenorphine/naloxone
Others: Buprenorphine, butorphanol, nalbuphine, pentazocine, pentazocine/acetaminophen, pentazocine/naloxone

◉ Buprenorphine/Naloxone

Brand Name

Suboxone, Bunavail, Zubsolv

Generic Name

Buprenorphine/naloxone

Rx Only

Class III controlled substance

Dosage Forms

Sublingual film, buccal film, sublingual tablet

Usage

Maintenance treatment for opioid dependence

Pregnancy Category C

Dosing

- Induction: Sublingual film (Suboxone)
  - Day 1 induction: Initial: Sublingual buprenorphine 2 mg/naloxone 0.5 mg or buprenorphine 5 mg/naloxone 1 mg. May titrate dose based on control of acute withdrawal symptoms approximately every 2 hours up to a total dose of buprenorphine 8 mg/naloxone 2 mg
    - Titrate dose in increments of buprenorphine 2 mg/naloxone 0.5 mg or buprenorphine 4 mg/naloxone 1 mg
  - Day 2 induction: Up to buprenorphine 16 mg/naloxone 4 mg once daily
- Induction: Sublingual tablet (Zubsolv)
  - Day 1 induction: Initial: Sublingual buprenorphine 1.4 mg/naloxone 0.36 mg or buprenorphine 2.9 mg/naloxone 1 mg. May titrate dose based on control of acute withdrawal symptoms every 1.5 to 2 hours up to a total day 1 dose of buprenorphine 5.7 mg/naloxone 1.4 mg
    - Titrate dose in increments of buprenorphine 1.4 mg/naloxone 0.36 mg or buprenorphine 2.9 mg/naloxone 0.71 mg
  - Day 2 induction: Up to buprenorphine 11.4 mg/naloxone 2.9 mg once daily
- Maintenance: Buccal film (Bunavail)
  - Usual dose: Buprenorphine 8.4 mg mg/naloxone 1.4 mg once daily
    - Adjust dose in increments/decrements of buprenorphine 2.1 mg/naloxone 0.3 mg to a level that maintains treatment and suppresses opioid withdrawal symptoms
    - Usual range: Buprenorphine 2.1–12.5 mg/naloxone 0.3–2.1 mg once daily
- Maintenance: Sublingual film (Suboxone) and sublingual tablet (Suboxone)
  - Target dose: Buprenorphine 16 mg/naloxone 4 mg once daily
    - Adjust dose in increments/decrements of buprenorphine 2 mg/naloxone 0.5 mg or buprenorphine 4 mg/naloxone 1 mg to a level that maintains treatment and suppresses opioid withdrawal symptoms
    - Usual range: Buprenorphine 4–24 mg/naloxone 1–6 mg once daily
- Maintenance: Sublingual tablet (Zubsolv)

- Target dose: Buprenorphine 11.4 mg mg/naloxone 2.9 mg once daily
  - Adjust dose in increments/decrements of buprenorphine 1.4 mg/naloxone 0.36 mg or buprenorphine 2.9 mg/naloxone 0.71 mg to a level that maintains treatment and suppresses opioid withdrawal symptoms
  - Usual range: Buprenorphine 2.9–17.2 mg/naloxone 0.71–4.2 mg once daily
- Hepatic dosage adjustment:
  - Mild hepatic impairment: No dosage adjustment necessary
  - Moderate hepatic impairment: Not recommended for use during induction therapy. Use with caution during maintenance treatment (due to reduced clearance of naloxone and potential reduction in efficacy of buprenorphine).
  - Severe hepatic impairment: Use is not recommended.

Adverse Reactions: Most Common

Drowsiness, dizziness, headache, CNS depression

Adverse Reactions: Rare/Severe/Important

Hepatitis, orthostatic hypotension

Major Drug Interactions

Drugs Affecting Buprenorphine/Naloxone

- Sedatives and alcohol: Increase CNS depression

Buprenorphine/Naloxone's Effect on Other Drugs

- Opioid analgesics: Decreases the therapeutic effect of opioids; can precipitate withdrawal in opioid-dependent patients
- Selective serotonin reuptake inhibitors (SSRIs): Increases serotonergic effect; may cause serotonin syndrome

Essential Monitoring Parameters

- LFTs: Baseline and periodically during treatment
- Respiratory status
- Mental status
- CNS depression
- Symptoms of withdrawal
- Signs of addiction, use, or misuse

Counseling Points

- Avoid activities that require mental alertness (e.g., driving, operating machinery) until the effects of the medication are known and comfortable. Follow this advice whenever the dose is increased.
- Buccal film: Prior to placing the film, moisten the inside of the cheek with water or saliva. Apply film with a dry finger immediately upon removal from the packaging. Ensure that the surface containing text is placed against the inside of the moistened cheek. Press and hold in place with finger for 5 seconds. Keep film in place until it dissolves completely. Do not chew, swallow, or move film after placement. Food and liquids can be consumed after the film has dissolved completely. Do not cut or tear the film.
  - Bunavail: If more than one film is required at one time, the additional film should be placed on the inside of the other cheek. Do not apply more than 2 films to the inside of one cheek at a time.
  - Suboxone: If a third film is necessary, place it on the inside of the right or left cheek after the first two films have dissolved.
- Sublingual film: Place one sublingual film under the tongue until it dissolves completely, close to the base on the left or right side; it should not be cut, swallowed, chewed, or moved after placement. If more than one film is needed, the second film should be placed under the tongue on the opposite side; minimize overlapping. If a third film is necessary to achieve the prescribed dose, place it under the tongue on either side, after the first two films have dissolved.
- Sublingual tablet: Place the sublingual tablet under the tongue until it dissolves completely; it should not be swallowed. If two or more tablets are needed per dose, all can be placed under the tongue together or they can be placed two at a time. To maintain consistent bioavailability, subsequent doses should be taken the same way. Avoid fluids or food until the tablet(s) is/are completely dissolved.
  - Zubsolv: In patients requiring more than one sublingual tablet, place all tablets in different places under the tongue at the same time.

Key Points

- An FDA-approved patient medication guide must be dispensed with this medication
- The same dose should be used when switching between sublingual tablets and sublingual film. Caution should be exercised because the sublingual film has a potential for greater bioavailability; monitor patients closely when changing formulations for changes in mental (respiratory) status or withdrawal.
- Only physicians with a registered DEA number for buprenorphine/naloxone can prescribe it
- Buprenorphine sublingual tablets are preferred during the induction phase. Buprenorphine/naloxone can be used during the induction phase for short-acting opioids or heroin but is not recommended for use during the induction period for long-acting opioids or methadone. Initiate treatment when signs of moderate opioid withdrawal appear and not less than 6 hours after last opioid use. Titrate to adequate maintenance dose as quickly as possible based on withdrawal symptom control.

ANTICHOLINERGICS, ANTI-PARKINSON'S AGENTS

Introduction

Anticholinergic agents are used in the treatment of Parkinson's disease and to relieve the parkinsonian signs of antipsychotic agent–induced extrapyramidal symptoms (EPS). Their use in the treatment of EPS has decreased since the introduction of atypical antipsychotic agents. These agents should be used with caution due to the risk of anticholinergic adverse effects.

Mechanism of Action for the Drug Class

These agents decrease the activity of acetylcholine to balance out the production of dopamine and acetylcholine. They may inhibit the reuptake and storage of dopamine, thereby prolonging the action of dopamine.

Members of the Drug Class

In this section: Benztropine
Others: Trihexyphenidyl, procyclidine

◉ Benztropine

Brand Name

Cogentin

Generic Name

Benztropine

Rx Only

Dosage Forms

Tablet, injection

Usage

Adjunctive treatment of Parkinson's disease, treatment of drug-induced EPS (except tardive dyskinesia)

Pregnancy Category B

Dosing

- Parkinsonism: Oral/IM/IV: Initial dose 1–2 mg/day at bedtime or in 2 to 4 divided doses. Titrate to 0.5–6 mg/day.
  - Initiate at lower dosage and increase gradually until relief or a maximum dose of 6 mg/day
- Drug-induced EPS: Oral/IM/IV initial dose is 1–2 mg 2 to 3 times daily. Titrate to1–4 mg once or twice daily.
- May be given IV, but typically administered IM in patients who cannot take orally

Adverse Reactions: Most Common

Tachycardia, constipation, nausea, xerostomia, blurred vision, urinary retention

Adverse Reactions: Rare/Severe/Important

Heat stroke, anhidrosis, hyperthermia, paralytic ileus, confusion, increased intraocular pressure, mood or mental changes, visual hallucinations

Major Drug Interactions

Drugs Affecting Benztropine

- Agents with anticholinergic activity: Additive anticholinergic side effects
- Ethanol: Increases CNS depression

Benztropine's Effect on Other Drugs

- Potassium chloride: Increases risk of GI lesions

Contraindications

Pyloric or duodenal obstruction, stenosing peptic ulcers, bladder neck obstructions, achalasia, myasthenia gravis, closed-angle glaucoma, children < 3 years of age

Essential Monitoring Parameters

- Anticholinergic effects, heart rate

Counseling Points

- This drug may impair heat regulation; use caution when engaging in activities that lead to increased body temperature
- May cause drowsiness, dizziness, and blurry vision
- Avoid alcohol use

Key Points

- Because anticholinergic side effects are common with this medication, it should not be used long term
- Use with caution in older patients due to an increased risk of confusion and hallucinations
- Benztropine is most effective for relieving tremor and/or rigidity rather than bradykinesia
- Benztropine does not improve and may aggravate tardive dyskinesia. It should be avoided in patients with the condition.

ANTICHOLINERGICS, ANTIHISTAMINE ANTIEMETICS

Introduction

The medications in this drug class are antihistamines used to treat and prevent nausea and vomiting due to motion sickness. Meclizine is readily available over the counter for patient self-treatment.

Mechanism of Action for the Drug Class

Antihistamine antiemetics consist of first-generation antihistamines, which non-selectively antagonize H1 receptors and block vasodepressor response to histamine. Drugs in this class are centrally acting agents with anticholinergic, antihistaminic, and antiemetic activity, which decrease the excitability of the labyrinth of the middle ear and block conduction of the middle ear vestibular pathways. This reduces nausea and vomiting associated with motion sickness.

Members of the Drug Class

In this section: Meclizine, Promethazine
Others: Cyclizine, dimenhydrinate, promethazine, hydroxyzine

⦿ Meclizine

Brand Names

Antivert, Bonine (OTC), Dramamine Less Drowsy Formula (OTC), Trav-L-Tabs (OTC)

Generic Name

Meclizine

Rx and OTC

Dosage Forms

Tablet, chewable tablet

Usage

Prevention and treatment of motion sickness and vertigo

Pregnancy Category B

Dosing

- Motion sickness: For adults and children ≥ 12 years of age, 25–50 mg 1 hour before travel; repeat if necessary at 24-hour intervals
- Vertigo: 25–100 mg daily in divided doses, depending on clinical response
- Renal dosage adjustment: There are no dosage adjustments provided in manufacturer's labeling. Use with caution in patients with renal impairment
- Hepatic dosage adjustment: There are no dosage adjustments provided in manufacturer's labeling. Use with caution in patients with hepatic impairment.

Adverse Reactions: Most Common

Drowsiness, somnolence, xerostomia, constipation, headache

Adverse Reactions: Rare/Severe/Important

Cholestatic jaundice, blurry vision, auditory and visual hallucinations

Major Drug Interactions

Drugs Affecting Meclizine

- CNS depressant agents: Additive sedation
- Anticholinergic agents: Additive anticholinergic effects

Essential Monitoring Parameters

- No routine laboratory tests are recommended
- Monitor for side effects, including CNS depression

Counseling Points

- Meclizine may impair the ability to perform hazardous activities requiring mental alertness or physical coordination, including driving and operating heavy machinery
- Avoid alcohol and other CNS depressants while using meclizine

Key Points

- Meclizine should only be used for mild to moderate motion sickness because other medications are more effective for severe conditions
- Exclusions for self-care include signs of dehydration (including lethargy and decreased urine output), hematemesis, dyspnea, tachycardia, chemotherapy-induced nausea, and vomiting, vomiting lasting longer than 24 hours in children or 48 hours in adults, recent head trauma, suspected poisoning, and vomiting accompanied by fever, diarrhea, severe headaches, or stiff neck
- Meclizine is more effective for prevention rather than treatment of motion sickness
- Drowsiness is a common side effect of meclizine, even though this ingredient is found in OTC products marked as "Non-Drowsy"
- Meclizine should not be used in children younger than 12 years of age
- Meclizine is included in the American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Use caution in patients over 65 years of age.

⦿ Promethazine

Brand Names

Phenadoz, Phenergan, Promethegan

Generic Name
Promethazine

Rx Only

Dosage Forms
Tablet, injection, oral solution/syrup, rectal suppository

Usage
Treatment of nausea and vomiting, allergic conditions, motion sickness, surgical analgesia, and sedation

Pregnancy Category C

Dosing (adults)
- Nausea and vomiting: Oral/IM/IV/rectal: 12–25 mg every 4 to 6 hours
- Allergic conditions: Oral/rectal: 25 mg at bedtime or 6.25–12.5 mg three times daily IM/IV: 25 mg once, may repeat in 2 hours
- Motion sickness: Oral/rectal: 25 mg 30 to 60 minutes before departure, repeat in 8 to 12 hours, as needed
- Surgical analgesia and sedation: IM/IV: 25–50 mg/dose

Adverse Reactions: Most Common
Drowsiness, photosensitivity, bradycardia, hypotension, anticholinergic effects

Adverse Reactions: Rare/Severe/Important
Severe chemical irritation and damage to tissues with IV use, respiratory depression, neuroleptic malignant syndrome, extrapyramidal symptoms

Major Drug Interactions
- Drug's affecting promethazine: Metoclopramide can enhance toxicity of promethazine
- Promethazine's effect on other drugs: Additive effects with other anticholinergic drugs, may enhance serotonergic effects of serotonin modulators, may enhance the effects of CNS depressants, can decrease efficacy of nitroglycerin, can enhance ulcerogenic effect of oral potassium chloride

Contraindications
Subcutaneous or intra-arterial administration, Children < 2 years of age, respiratory illness

Essential Monitoring Parameters
- Mental status changes, CNS effects
- Signs of tissue injury with IV use

Counseling Points
- Avoid alcohol and use of other CNS depressants
- Avoid prolonged sun exposure
- Promptly report any injection-site pain within days of receiving an intravenous infusion

Key Points
- **Black Box Warnings:**
  - Do not use in patients < 2 years old due to potential for fatal respiratory depression. Use of intravenous administration can cause severe tissue injury including gangrene.
  - IV promethazine must be diluted and run via a large bore vein. Infusion time of at least 10 to 15 minutes preferred.
  - Deep IM is the preferred parenteral route

ANTICHOLINERGICS

Introduction
Scopolamine is a belladonna alkaloid, which is a naturally occurring anticholinergic agent used for the prevention of nausea and vomiting from motion sickness or following anesthesia.

Mechanism of Action of the Drug Class
Scopolamine acts as a competitive inhibitor at postganglionic muscarinic receptor sites of the parasympathetic nervous system and on smooth muscles that respond to acetylcholine. Scopolamine acts on the central nervous system by blocking cholinergic transmission from the vestibular nuclei and from the reticular formation to the vomiting center. As a result, this agent can inhibit the secretion of saliva and sweat, decrease gastrointestinal secretions and motility, and depress motor function.

Members of the Drug Class
In this section: Scopolamine

◉ Scopolamine

Brand Name
Transderm-Scop

Generic Name
Scopolamine

Rx Only

Dosage Forms
Transdermal patch (scopolamine hydrobromide injection is no longer available in the United States)

Usage

Scopolamine is used for the prevention of nausea and vomiting associated with motion sickness and recovery from anesthesia and surgery. It can also be used for breakthrough treatment of nausea and vomiting associated with chemotherapy (off label).

Pregnancy Category C

Dosing

- The transdermal system delivers approximately 1 mg of scopolamine over 72 hours
- Motion sickness: Apply one patch to hairless area behind one ear at least 4 hours prior to exposure. If therapy is required for longer than72 hours, the first patch should be removed and a fresh one placed on the hairless area behind the other ear.
- Postoperative nausea and vomiting: Apply one patch to hairless area behind one ear the night before surgery. For Caesarean section, apply the patch 1 hour prior to surgery, to minimize exposure of the infant to the drug. Remove 24 hours after surgery.

Adverse Reactions: Most Common

Xerostomia, drowsiness, dizziness, urinary retention, agitation, transient impairment of eye accommodation, pharyngitis, application-site burning, redness, or rashes

Adverse Reactions: Rare/Severe/Important

Acute toxic psychosis, glaucoma

Major Drug Interactions

Drugs Affecting Scopolamine

- CNS depressant agents: Additive sedation
- Anticholinergic agents: Additive anticholinergic effects

Scopolamine's Effect on Other Drugs

- The absorption of oral medications may be decreased during the concomitant use of scopolamine because of decreased gastric motility and delayed gastric emptying.

Contraindication

Narrow angle glaucoma or angle closure glaucoma

Essential Monitoring Parameters

- Heart rate, urinary output, intraocular pressure

Counseling Points

- Place the patch on a clean, dry, hairless area behind one ear. Do not apply to an area with scars, cuts, or irritation.
- Only use 1 patch at a time
- Do not cut the patch and avoid touching the metallic sticky surface of the patch with your hands
- Wash hands thoroughly after handling the patch and avoid contact with eyes
- Wear the patch continuously; avoid removing and reapplying the patch during the 72-hour period. If the patch becomes displaced, it should be discarded, and a fresh one should be placed on the hairless area behind the other ear.
- After removing a used patch, fold the patch in half with the sticky sides together prior to disposing, out of the reach of children and pets
- Can be worn during bathing/showering
- Use with caution if participating in underwater sports as disorientation is possible
- Avoid participating in activities that require mental alertness or drinking alcohol, as scopolamine may cause drowsiness, disorientation, and confusion
- May cause dry mouth; may use hard candy or ice chips to alleviate
- May contain metal; remove prior to MRI to avoid skin burns

Key Points

- Scopolamine (hyoscine) hydrobromide should not be interchanged with scopolamine butylbromide (a Canadian product), as dosages are not equivalent
- The scopolamine patch should be applied at least 4 hours prior to exposure and can be worn for 3 days. A new patch can be applied behind the opposite ear if ongoing protection is needed.
- Scopolamine should be applied the evening before surgery and should be kept in place for 24 hours following surgery
- Withdrawal symptoms of dizziness, nausea, vomiting, abdominal cramps, sweating, headache, confusion, muscle weakness, and equilibrium disturbances may appear 24 or more hours after the patch has been removed
- Only one patch should be worn at any time
- Scopolamine is included in the American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Use caution in patients over 65 years of age.

ANTIDOTE, ACETYLCYSTEINE

Introduction

Acetylcysteine is an antidote used to treat acute acetaminophen overdose-induced hepatotoxicity and to prevent contrast–induced nephropathy (CIN). It is also used for its mucolytic properties.

Mechanism of Action for Acetylcysteine

Acetylcysteine is an antidote for acute acetaminophen toxicity and is considered to be hepatoprotective by maintaining and restoring hepatic concentrations of glutathione. Glutathione is needed to inactivate a hepatotoxic metabolite of acetaminophen. Its mucolytic action is due to its ability to open disulfide bonds in mucoproteins, therefore, decreasing the viscosity of the mucus. The presumed mechanism in preventing CIN is its ability to scavenge oxygen-derived free radicals and improve endothelium-dependent vasodilation.

Members of the Drug Class

In this section: Acetylcysteine
Others: Mucomyst, Dornase alfa

◉ Acetylcysteine

Brand Name

Acetadote, Cetylev

Generic Name

Acetylcysteine, N-Acetylcysteine

Rx Only

Dosage Forms

Injection, solution, oral inhalation, effervescent tablet

Usage

Acetaminophen overdose, prevention of contrast induced nephropathy, adjunctive mucolytic agent in patients with viscous mucous secretions, distal intestinal obstruction syndrome

Pregnancy Category

Adverse events have not been observed in animal reproduction studies. Based on limited reports using acetylcysteine to treat acetaminophen overdose in pregnant women, acetylcysteine has been shown to cross the placenta and may provide protective concentrations in the fetus. Acetylcysteine may be used to treat acetaminophen overdose during pregnancy. In general, medications used as antidotes should take into consideration benefits vs risks.

Dosing

- Acetaminophen overdose:
  - 72-hour PO regimen effervescent tablets or solution for oral administration:
    - Total number of doses: 18 (total dose is 1330 mg/kg)
    - Loading dose: 140 mg/kg
    - Maintenance dose: 70 mg/kg every 4 hours; repeat dose if emesis occurs within 1 hour of administration
  - 21-hour IV regimen:
    - Total number of doses: Three (total dose is 300 mg/kg)
    - Loading dose: 150 mg/kg (maximum dose: 15 g) infused over 1 hour
    - Second dose: 50 mg/kg (maximum dose: 5 g) infused over 4 hours
    - Third dose: 100 mg/kg (maximum dose: 10 g) infused over 16 hours
- Prevention of CIN:
  - 1200 mg PO twice daily for 2 days (regimen should be started the day before the procedure) for a total of four doses

Adverse Reactions: Most Common

Nausea, vomiting, anaphylactoid reaction, flushing, erythema, tachycardia,

Adverse Reactions: Rare/Severe/Important

Anaphylaxis, angioedema, bronchospasm (oral inhalation), chest tightness, gastrointestinal hemorrhage

Major Drug Interactions

No known significant drug interactions

Essential Monitoring Parameters

Acetaminophen overdose: Monitor patient for the development of anaphylaxis or anaphylactoid reactions; monitor serum acetaminophen concentrations, AST, ALT, bilirubin, PT, INR, serum creatinine, BUN, serum glucose, hemoglobin, hematocrit, and electrolytes. Assess patient for clinical status, nausea, vomiting, and skin rash following oral administration. Reassess LFTs for possible hepatotoxicity every 4 to 6 hours.

Counseling Point

May repeat oral acetylcysteine dose if vomiting occurs within 1 hour of ingestion

Key Points

- Itching, flushing, rash, and anaphylactoid reactions can occur with acetylcysteine. Patients should be continuously monitored in an inpatient setting when initiating acetylcysteine for acetaminophen overdose.
- For patients with acute acetaminophen ingestion, treatment should begin within 8 hours of ingestion or as soon as possible after ingestion. In patients with a suspected acute ingestion where the time of ingestion is unknown, the concentration is unobtainable, the patient presents > 8 hours after ingestion, or there is clinical evidence of toxicity, initiate treatment immediately and re-evaluate the need for acetylcysteine upon receipt of the results (if applicable).

ANTIDOTE, FLUMAZENIL

Introduction

Flumazenil is a benzodiazepine GABA receptor antagonist used most commonly for benzodiazepine overdose. It antagonizes the CNS effects of benzodiazepines. Caution should be used when administering flumazenil as it can precipitate benzodiazepine withdrawal (e.g., seizures) risks vs benefits should be assessed prior to initiation.

Mechanism of Action for Flumazenil

Flumazenil is a benzodiazepine antagonist. It competitively inhibits the receptor site on the GABA/benzodiazepine receptor complex, thus reversing the sedative effects of benzodiazepines.

Members of the Drug Class

In this section: Flumazenil
Others: None

◉ Flumazenil

Brand Name

Romazicon

Generic Name

Flumazenil

Rx Only

Dosage Form

Injection

Usage

Benzodiazepine overdose, reversal of general anesthesia, reversal of conscious sedation

Pregnancy Category C

Dosing

Benzodiazepine overdose (IV push doses given over 30 seconds):

- Initial dose: 0.2 mg over 30 seconds; if the desired level of consciousness is not obtained 30 seconds after the dose, 0.3 mg can be given over 30 seconds
- Repeat doses: 0.5 mg over 30 seconds repeated at 1-minute intervals
- Maximum total cumulative dose: 3 mg (usual total dose: 1–3 mg). Patients with a partial response at 3 mg may require (rare) additional titration up to a total dose of 5 mg (although doses > 3 mg do not reliably produce additional effects).

Adverse Reactions: Most Common

Vomiting, flushing, dizziness, sweating, headache, blurry vision

Adverse Reactions: Rare/Severe/Important

Seizures, extravasation, cardiac arrhythmias (e.g., ventricular tachycardias), and death (has occurred in patients who have ingested large amounts of tricyclic antidepressants as part of the overdose)

Major Drug Interactions

Flumazenil's Effect on Other Drugs

Nonbenzodiazepine hypnotics: May decrease sedative effects

Contraindications

Patients receiving benzodiazepines for potentially life-threatening condition (e.g., status epilepticus, control of intracranial pressure); tricyclic antidepressant overdose or in patients who are showing signs/symptoms of a tricyclic antidepressant overdose

Counseling Points

- Do not participate in activities requiring alertness for at least 24 hours after hospital discharge
- Avoid alcohol

Key Points

- Flumazenil can precipitate benzodiazepine withdrawal, including seizures
- Patients should be continuously monitored in an inpatient setting when receiving flumazenil
- Most patients respond to a cumulative dose of 1–3 mg IV of flumazenil
- Flumazenil does not antagonize the CNS effects of GABA agonists, which are not bound at the GABA/benzodiazepine receptor complex (e.g., ethanol, general anesthetics, and barbiturates) or reverse the effects of opioids

ANTIDOTE, NALOXONE

Introduction

Naloxone is an opioid reversal agent that is used as an antidote for opioid overdose

Mechanism of Action for the Drug Class

Naloxone is an opioid antagonist, which has the greatest affinity for μ receptors. It acts by competing for the μ, kappa, and opiate receptor sites in the CNS, displacing opioids at

the opioid receptor sites, and, therefore, antagonizing the analgesic, dysphoric, sedative, and other opioid pharmacologic effects.

Members of the Drug Class

In this section: Naloxone hydrochloride
Others: Naltrexone, alvimopan, methylnaltrexone

◉ Naloxone

Brand Name

Narcan, Evzio

Generic Name

Naloxone

Rx Only

Dosage Forms

Injection solution, nasal liquid

Usage

Acute opioid overdose, opioid-induced respiratory depression, opioid-induced depression, rapid detoxification in the management of opioid withdrawal, opioid-induced pruritus

Pregnancy Category C

Dosing

- General information
  - Routes of administration include IV (preferred), IM, SUB-Q, and intranasal
  - Naloxone should be used in combination with ACLS protocols
- Opioid overdose
  - Injectable: Narcan (IV, IM, SUB-Q)
    - Initial dose: 0.4–2 mg; repeat dose every 2 to 3 minutes, if needed
    - After reversal, readministration may be needed at a later time, depending on type and duration of opioid
    - Maximum dose: 10 mg (consider other causes of respiratory depression > 10 mg)
  - Injectable: Evzio (IM, SUB-Q)
    - Initial dose: 0.4 mg or 2 mg (contents of one auto-injector) as a single dose; repeat dose every 2 to 3 minutes, if needed, until emergency medical assistance becomes available
  - Intranasal: Narcan Nasal Spray
    - 4 mg (contents of one nasal spray) as a single dose; repeat dose every 2 to 3 minutes in alternating nostrils, if needed, until medical assistance becomes available
- Reversal of respiratory depression with therapeutic opioid doses:
  - Initial: 0.02–0.2 mg (IV), titrate to avoid serious withdrawal, seizures, arrhythmias, or severe pain; may repeat to a desired response (if dose > 0.8 mg, consider other causes of respiratory depression)

Adverse Reactions: Most Common

Nausea, vomiting

Adverse Reactions: Rare/Severe/Important

Acute opioid withdrawal (pain, hypertension, sweating, agitation, irritability)

Major Drug Interactions

No known significant drug interactions

Essential Monitoring Parameters

- Respiratory rate, heart rate, blood pressure, temperature, level of consciousness, ABGs, or pulse oximetry

Counseling Points

- Patients who received naloxone in the outpatient setting should seek immediate emergency medical assistance after the first dose due to the likelihood that respiratory and/or central nervous system depression will return
- Patients and family members/significant others should be trained in the use of naloxone in overdose
- Proper administration technique should be utilized (intended for buddy administration)

◉ Auto-Injector: (IM or SubQ) Intended for Buddy Administration

1. The person administering the medication should follow the printed instructions on the device or the electronic voice instructions coming from the speaker on the device (if the voice instruction system does not work, the device will still deliver the intended dose of naloxone when properly administered)
2. Administer IM or SubQ into the anterolateral aspect of the thigh; may be injected through clothing
3. Following proper administration, a red indicator appears in the viewing window; the needle is not visible before, during, or after the injection
4. Patients who received naloxone in the outpatient setting should seek immediate emergency medical assistance after the first dose due to the likelihood that respiratory and/or central nervous system depression will return

5. Repeat doses may be required until emergency medical assistance becomes available; a new device must be used as each device contains a single dose of naloxone

◉ Intranasal Spray: Intended for Buddy Administration

1. Do NOT prime or test the device prior to administration, administer as soon as possible
2. Administer in alternating nostrils with each dose
3. Place the patient in the supine position and provide support to the back of the neck to allow the head to tilt back
4. Following administration, turn the patient on his or her side
5. Each container has a single intranasal spray, do not reuse; if repeat administration is necessary, a new container must be used
6. Seek medical attention immediately

Key Points

- Naloxone may precipitate symptoms of opioid withdrawal (pain, hypertension, sweating, agitation, irritability)
- When used in the management of acute opiate overdose, because of the short duration of action of naloxone, resuscitative measures should be available (e.g., maintenance of an adequate airway, ACLS)
- The goal of naloxone treatment in the postoperative setting is to reverse the excessive opioid effect without completely reversing the analgesic effect of the opioid, which could lead to increased pain
- Consider using an IV continuous infusion in patients with an exposure to long-acting opioids (e.g., methadone) or sustained-release products

ANTIGOUT AGENT, COLCHICINE

Introduction

Colchicine is an antimitotic drug that is effective at relieving acute gout attacks. It possesses weak anti-inflammatory and antigout properties.

Mechanism of Action for the Drug Class

The specific mechanism of action of colchicine is unknown. However, it is thought that colchicine binds to beta-tubulin, a microtubular protein, causing its depolymerization and preventing activation and migration of neutrophils associated with mediating some gout symptoms. Its anti-inflammatory property regarding gout appears to be due to its ability to decrease leukocyte motility, phagocytosis, and lactic acid production, therefore, decreasing the deposition of urate crystals in the joints.

Members of the Drug Class

In this section: Colchicine Others: None

◉ Colchicine

Brand Name

Colcrys, Mitigare

Generic Name

Colchicine

Rx Only

Dosage Form

Tablet

Usage

Treatment and prophylaxis of acute gout attacks, treatment of familial Mediterranean fever, pericarditis post-STEMI, recurrent autoimmune or idiopathic pericarditis

Pregnancy Category C

Dosing

- Gout:
  - Prophylaxis:
    - Initial dose in adults and adolescents older than 16 years of age: 0.6 mg orally once or twice daily
    - Maximum dose: 1.2 mg/day
  - Treatment of acute attacks:
    - Initial dose in adults and adolescents older than 16 years of age: 1.2 mg at first sign of a

flare, followed by 0.6 mg 1 hour later. Following administration of acute colchicine treatment dose, wait 12 hours before resuming a prophylactic colchicine dose.
    - Maximum dose: 1.8 mg within 1 hour
- Familial Mediterranean fever: Give total daily dose in 1 or 2 divided doses. Increase or decrease dose as indicated and as tolerated in increments of 0.3 mg/day, not to exceed the maximum recommended daily dose.
  - Adults and children older than 12 years of age: 1.2–2.4 mg daily
  - Children 6 to 12 years of age: 0.9–1.8 mg daily
  - Children 4 to 6 years of age: 0.3–1.8 mg
- Renal dosage adjustment:
  - Prophylaxis of gout flares
    - Mild (CrCl 50–80 ml/min) to moderate (CrCl 30–50 ml/min) renal function impairment: Dosage adjustment not required; monitor patients for adverse events
    - Severe renal impairment (CrCl < 30 ml/min): Initial dose of 0.3 mg/day; use with caution if titrating dose and monitor for adverse effects
    - Hemodialysis: Starting dose of 0.3 mg given twice per week with close monitoring for adverse effects
  - Treatment of gout flares
    - Mild (CrCl 50–80 ml/min) to moderate (CrCl 30–50 ml/min) renal function impairment: Dosage adjustment not required; monitor patients for adverse events
    - Severe renal impairment (CrCl < 30 ml/min): Dosage adjustment not required; however, do not repeat treatment course more than once every 2 weeks
    - Hemodialysis: Total recommended dose of 0.6 mg; do not repeat treatment course more than once every 2 weeks, as hemodialysis does not remove it
  - Treatment of gout flare is not recommended in patients receiving prophylactic colchicine in patients with renal impairment
  - Familial Mediterranean fever
    - Mild (CrCl 50–80 ml/min) to moderate (CrCl 30–50 ml/min) renal function impairment: Dose reduction may be necessary; monitor patients for adverse events
    - Severe renal impairment (CrCl < 30 ml/min): Initial dose of 0.3 mg/day; use with caution if titrating dose and monitor for adverse effects
    - Hemodialysis: Total recommended starting dose should be 0.3 mg/day with close monitoring for adverse effects
- Hepatic dosage adjustment:
  - Prophylaxis of gout flares
    - Mild-to-moderate hepatic impairment: Dosage adjustment not required; monitor patients for adverse events
    - Severe hepatic impairment: Consider dosage adjustment.
  - Treatment of gout flares
    - Mild-to-moderate hepatic impairment: Dosage adjustment not required; monitor patients for adverse events
    - Severe hepatic impairment: Dosage adjustment not required; do not repeat treatment course more than once every 2 weeks
    - Treatment of gout flare is not recommended in patients receiving prophylactic colchicine who have hepatic impairment
  - Familial Mediterranean fever
    - Mild-to-moderate hepatic impairment: Monitor patients for adverse events
    - Severe hepatic impairment: Consider dosage adjustment

Adverse Reactions: Most Common

Nausea, vomiting, diarrhea

Adverse Reactions: Rare/Severe/Important

Myelosuppression, neuromyopathy, aplastic anemia, hepatotoxicity

Major Drug Interactions

Drugs Affecting Colchicine

- CYP3A4 and P-glycoprotein inhibitors (i.e., azole antifungals, cyclosporine, macrolides, diltiazem, verapamil, protease inhibitors): Increase concentrations and increase risk of toxicity
- Digoxin: Increases concentration
- P-glycoprotein inducers: Decrease concentration and effectiveness

Colchicine's Effect on Other Drugs

- HMG-CoA reductase inhibitors: Increases risk of myopathy and rhabdomyolysis
- Fibric acid derivatives: Increases risk of myopathy rhabdomyolysis

Contraindications

Concomitant use of P-glycoprotein or strong CYP3A4 inhibitors in the presence of hepatic or renal impairment
Mitigare only: Patients with both renal and hepatic impairment

Essential Monitoring Parameters

- Renal and hepatic function
- CBC

Counseling Points

- Read the medication guide that comes with colchicine before you start taking this medication and each time you get a refill
- Foods and drinks containing high amounts of purines (for example, organ meats, red meat, high-fat dairy, fish, and beer) can increase your risk for a

gout attack. Limit purine-rich food and stay hydrated to decrease the frequency of gout attacks.
- Avoid grapefruit and grapefruit juice; it can increase the amount of colchicine in your body and your risk for side effects
- Many drugs may interact with colchicine. Check with your healthcare team before starting any new medications, especially antibiotics.
- Immediately report muscle pain or weakness, tingling, or numbness in fingers or toes to your healthcare team

Key Points

- Colchicine must be dispensed with the FDA-approved medication guide
- Colchicine is recommended upon initiation of gout flare prophylaxis with uric acid-lowering therapy, to minimize the risk for gout flares due to changing serum uric acid levels and mobilization of urate from tissue deposits. Prophylactic colchicine therapy may be beneficial for at least the first 6 months of uric acid-lowering therapy.
- Dose adjustment is recommended in patients with hepatic and renal dysfunction
- Doses need to be adjusted if used in combination with CYP3A4 inhibitors and p-glycoprotein inhibitors. Concurrent use with strong CYP3A4 inhibitors and p-glycoproteins are contraindicated in renal and hepatic impairment. The manufacturer's prescribing information contains dose modification recommendations during the coadministration of interacting drugs.
- The most common side effect of colchicine is diarrhea. Lower doses may help to decrease GI side effects.

ANTIHYPERURICEMIC AGENTS, ANTIGOUT AGENTS

Introduction

Xanthine oxidase inhibitors are used to treat primary hyperuricemia of gout and hyperuricemia secondary to high uric acid levels in patients receiving chemotherapy. This drug class is also used to prevent gout attacks.

Mechanism of Action for the Drug Class

Xanthine oxidase inhibitors decrease the production of uric acid by blocking the action of xanthine oxidase, an enzyme that converts hypoxanthine to xanthine and then xanthine to uric acid. Allopurinol is metabolized to oxypurinol, which is also an inhibitor of xanthine oxidase. Allopurinol and oxypurinol are analogs of purine and pyrimidines and can affect the metabolic pathways of both. This inhibits the synthesis of pyrimidines, which are used for RNA and DNA synthesis. Febuxostat is not a purine analog and does not impact enzyme activity involved in purine or pyrimidine synthesis or metabolism.

Members of the Drug Class

In this section: Allopurinol, Febuxostat

◉ Allopurinol

Brand Names

Zyloprim, Aloprim

Generic Name

Allopurinol

Rx Only

Dosage Forms

Tablet, injection

Usage

Prevention of gout attacks, treatment of secondary hyperuricemia associated with chemotherapy *(tumor lysis syndrome),* prevention of recurrent calcium oxalate calculi

Pregnancy Category C

Dosing

- Gout: Adult dosing
  - Oral: Initial 100 mg once daily; increase at weekly intervals by increments of 100 mg/day as needed to achieve desired serum uric acid level
  - Mild gout:
    - Usual dosage range: 200–300 mg PO daily
  - Moderate-to-severe gout:
    - 400–600 mg PO daily
    - Oral doses > 300 mg should be given in divided doses
    - Maximum dose: 800 mg PO daily
- Hyperuricemia associated with chemotherapy:
  - Adult dosing:
    - Oral: 600–800 mg daily in divided doses for 2 to 3 days
    - IV: 200–400 mg/m^2 daily (maximum 600 mg daily) beginning 1 to 2 days before chemotherapy; IV daily doses can be given as a single infusion or in equally divided doses at 6-, 8-, or 12-hour intervals
  - Pediatric dosing:
    - Oral: Doses daily doses > 300 mg should be divided
      - Children < 6 years of age: 150 mg daily
      - Children 6 to 10 years of age: 300 mg daily

- Children > 10 years of age: Refer to adult dosing
  - IV: Starting dose 200 mg/m^2 daily beginning 1 to 2 days before chemotherapy; daily doses can be given as a single infusion or in equally divided doses at 6-, 8-, or 12-hour intervals
- Calcium oxalate stones (recurrent): Adult dosing
  - Oral: 200–300 mg daily in single or divided doses; may adjust dose as needed to control hyperuricosuria
  - IV: 200–400 mg/m^2 daily (maximum 600 mg daily) beginning 1 to 2 days before chemotherapy
- Renal dosage adjustment:
  - Initial dose of 50 mg/day may be considered in Stage 4 or worse CKD
  - CrCl 10–20 ml/min: 200 mg/day
  - CrCl 3–10 ml/min: Do not exceed 100 mg/day
  - CrCl < 3 ml/min: May need to extend dosing interval; do not exceed 100 mg/day
  - Hemodialysis: Allopurinol and oxypurinol are dialyzable; initial dose of 100 mg on alternate days, given postdialysis. Increase cautiously to 300 mg based on response. If dialysis is daily, an additional 50% of the dose may be required postdialysis.
- Hepatic dosage adjustment: No adjustments provided in manufacturer's labeling

Adverse Reactions: Most Common

Maculopapular rash and pruritus, acute gout attack, diarrhea, nausea, increased LFTs

Adverse Reactions: Rare/Severe/Important

Rash, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), angioedema, agranulocytosis, aplastic anemia, eosinophilia, myelosuppression, thrombocytopenia, hepatitis, renal failure

Major Drug Interactions

Drugs Affecting Allopurinol

- ACE inhibitors, thiazide, and loop diuretics: Increase risk of hypersensitivity
- Uricosurics: Decrease effectiveness
- Antacids: Decrease absorption

Allopurinol's Effect on Other Drugs

- Azathioprine: Inhibits metabolism; reduce azathioprine dose by 66% to 75% to prevent severe myelosuppression
- Mercaptopurine: Inhibits metabolism; increases risk of myelosuppression; reduce mercaptopurine dose by 66% to 75%
- Didanosine: Inhibits metabolism, leading to increased concentrations
- Cyclosporine: Increases levels
- Amoxicillin/ampicillin: Increases risk of rash
- Warfarin: Enhances anticoagulant effect
- Carbamazepine: Increases levels

Contraindication

History of Allopurinol Hypersensitivity Syndrome

Essential Monitoring Parameters

- CBC
- Serum uric acid levels every 2 to 5 weeks during dose titration until desired level of < 6 mg/dl is achieved and every 6 months thereafter; some patients may require uric acid level < 5 mg/dl to control symptoms.
- LFTs periodically in patients with pre-existing hepatic disease
- Renal function (SrCr or CrCl) periodically
- Increased frequency of INR monitoring may be required for patients receiving concomitant warfarin therapy, especially upon initiation or dose titration of allopurinol
- Hydration status: fluid intake should be administered to yield an output of approximately 2 liters in adults

Counseling Points

- Your gout may flare up when you start taking allopurinol. Do not stop taking your allopurinol even if you have a flare. Your healthcare professional may give you other medications to help prevent your gout flares.
- Immediately stop taking allopurinol and contact your healthcare team if you experience a skin rash
- Maintain adequate hydration while taking allopurinol
- Avoid alcohol, caffeine, and large amounts of vitamin C during therapy (large amounts of vitamin C may increase the chances of kidney stone formation)
- Take allopurinol with food to minimize stomach upset
- Report any fever, sore throat, painful urination, blood in urine, and/or swelling of mouth or lips to your healthcare provider
- Periodic blood tests may be ordered to monitor for effectiveness and side effects

Key Points

- Allopurinol is not recommended for the treatment of asymptomatic hyperuricemia
- Peak efficacy may be delayed for 2 to 6 weeks. Colchicine is recommended upon initiation of gout flare prophylaxis with uric acid-lowering therapy, such as allopurinol, to minimize the risk for gout flares due to changing serum uric acid levels and mobilization of urate from tissue deposits. Prophylactic colchicine therapy may be beneficial for at least the first 6 months of uric acid-lowering therapy.
- Fluid intake should be administered to yield an output of approximately 2 liters in adults
- Rash is a common adverse reaction that can occur any time during therapy. Rash can be followed by severe hypersensitivity reactions. Discontinue immediately at onset of rash. Allopurinol may be reintroduced at a dose of 50 mg/day following recovery from mild reactions. If rash recurs, discontinue allopurinol permanently.

- Generalized hypersensitivity involving severe skin reactions, fever, chills, nausea, vomiting, arthralgia, and/or eosinophilia resembling Stevens-Johnson syndrome have occurred. Associated vasculitis and tissue response may present as hepatitis, interstitial nephritis, and very rarely, epilepsy. This may occur at any time during treatment. Discontinue allopurinol immediately and permanently at onset of any of these symptoms. Risk may be increased in the setting of renal and/or hepatic disorders. Corticosteroids may be beneficial in overcoming such reactions.
- Reduce dosage in renal failure

Febuxostat

Brand Names
Uloric

Generic Name
Febuxostat

Rx Only

Dosage Form
Tablet

Usage
Chronic management of hyperuricemia in patients with gout

Pregnancy Category C

Dosing
- Hyperuricemia:
  - Initial: 40 mg once daily; may increase to 80 mg once daily in patients who do not achieve a serum uric acid level < 6 mg/dl after 2 weeks
  - Maximum dose: 120 mg once daily
- Renal dosage adjustment: No dosage adjustment is necessary in mild-to-moderate renal impairment
- Hepatic dosage adjustment: No dosage adjustment is necessary in mild-to-moderate hepatic impairment

Adverse Reactions: Most Common
Increased LFTs, nausea

Adverse Reactions: Rare/Severe/Important
Angioedema, atrial fibrillation, atrial flutter, cerebral infarction, cerebrovascular accident, hepatic failure, myocardial infarction, hypersensitivity, and serious skin reactions, such as Stevens Johnson syndrome and DRESS

Major Drug Interactions
Drugs Affecting Febuxostat

No significant interactions known

Febuxostat's Effect on Other Drugs

Azathioprine, didanosine, mercaptopurine, theophylline: Increase levels

Contraindication
Concomitant use of azathioprine or mercaptopurine

Essential Monitoring Parameters
- Serum uric acid levels every 2 to 5 weeks during dose titration until desired level of < 6 mg/dl is achieved and every 6 months thereafter; some patients may require uric acid level < 5 mg/dl to control symptoms
- LFTs at baseline, 2 months, 4 months, and periodically thereafter
- Signs and symptoms of MI or stroke
- Signs and symptoms of hypersensitivity or severe skin reactions

Counseling Points
- Do not take febuxostat if you take azathioprine or mercaptopurine
- Immediately stop taking febuxostat and contact your healthcare team if you experience any skin rash or swelling of the lips or mouth
- Your gout may flare up when you start taking febuxostat. Do not stop taking your febuxostat, even if you have a flare. Your healthcare professional may give you other medications to help prevent your gout flares.

Key Points
- Febuxostat is not recommended for the treatment of asymptomatic hyperuricemia.
- Colchicine is recommended upon initiation of gout flare prophylaxis with uric acid-lowering therapy, such as febuxostat, to minimize the risk for gout flares due to changing serum uric acid levels and mobilization of urate from tissue deposits. Prophylactic colchicine therapy may be beneficial for at least the first 6 months of uric acid-lowering therapy. If a gout flare occurs, febuxostat does not need to be discontinued.

ELECTROLYTE SUPPLEMENTS

Introduction

Potassium is a major intracellular electrolyte that is essential for the conduction of nerve impulses and contraction of skeletal, cardiac, and smooth muscle. The body requires appropriate amounts of potassium to function properly. Potassium chloride is the most common potassium formulation used when replenishing potassium.

Mechanism of Action for the Drug Class

Potassium is the major intracellular cation and is essential for the conduction of nerve impulses in the heart, brain, and skeletal muscle. Potassium maintains intracellular tonicity; contractility of cardiac, skeletal, and smooth muscle; acid–base balance; gastric secretion; and carbohydrate metabolism.

Members of the Drug Class

In this section: Potassium chloride
Others: potassium phosphate, potassium acetate, potassium bicarbonate, potassium citrate, potassium gluconate, potassium iodide

◉ Potassium Chloride

Brand Names

Klor-Con, Micro-K, K-Tab

Generic Name

Potassium chloride

Dosage Forms

Tablet, capsule, powder, liquid, injection

Rx Only

Usage

Treatment and prevention of hypokalemia

Pregnancy Category C

Dosing

- Prevention of hypokalemia (e.g., due to diuretic therapy):
  - Oral: 20–40 mEq daily in 1 to 2 divided doses
- Treatment of hypokalemia:
  - Oral:
    - Limit dose to 20–40 mEq to minimize GI adverse effects
    - Initial dose: 10–40 mEq, depending on the severity of hypokalemia
  - Intermittent IV infusion:
    - Continuous ECG monitoring and IV infusion via central line is highly recommended in infusion rates > 10 mEq/hour
    - Variability exists in dosing and infusion rate recommendations; therapy should be patient specific and based on institutional guidelines
    - Maximum infusion rate (via central line only): 40 mEq/hour in presence of continuous ECG monitoring and frequent lab monitoring
- Frequent lab monitoring should occur after repletion to avoid hyperkalemia and dosing recommendations should be patient specific and based on institutional guidelines (when applicable)
- Dosing in renal impairment: Reduce initial dose by at least 50% in patients with renal impairment

Adverse Reactions: Most Common

Nausea, vomiting, diarrhea, flatulence (more common with oral repletion), hyperkalemia

Adverse Reactions: Rare/Severe/Important

Cardiac arrest, ECG abnormalities, heart block, asystole, ventricular arrhythmias, abdominal pain (oral formulation), GI ulcer (oral formulation), extravasation (IV formulation)

Major Drug Interactions

Potassium Chloride's Effect on Other Drugs

ACE inhibitors, angiotensin II receptor blockers, potassium-sparing diuretics: Increase risk of hyperkalemia

Contraindications

Hyperkalemia; solid oral dosage formulations are contraindicated in patients with structural, pathologic, and/or pharmacologic GI delay or immobility

Essential Monitoring Parameters

Serum potassium level, chloride, magnesium (to facilitate potassium repletion), cardiac monitor (if intermittent infusion or potassium infusion rates > 10 mEq/hour in adults); to assess adequate replacement, repeat serum potassium level 2 to 4 hours after dose

Counseling Points

- Oral potassium repletion: Doses should be taken with meals with a full glass of water to minimize GI irritation
- Sustained-release and wax-matrix products: Do not crush. These products should be swallowed whole.
- Powder formulations: May be diluted in water or juice
- Capsule formulations (e.g., Micro-K): Should be swallowed whole; however, capsules can be opened and sprinkled on applesauce or pudding

Key Points

- The potassium chloride concentrate for injection must be diluted before use. Numerous fatalities have occurred when patients were accidentally given undiluted potassium chloride concentrate.
- It is generally recommended to limit oral doses of potassium to 20–40 mEq/dose to avoid GI discomfort and adverse effects
- IV doses of potassium in an inpatient setting can be incorporated into the patient's maintenance IV fluids
  - Continuous ECG monitoring and IV infusion via central line is highly recommended in infusion rates > 10 mEq/hour
  - Variability exists in dosing and infusion rate recommendations; therapy should be patient specific and guided by institutional guidelines
  - The maximum infusion rate (via central line only) is 40 mEq/hour in the presence of continuous ECG monitoring and frequent lab monitoring
- Reduce the initial dose by at least 50% in patients with renal impairment
- Dosing recommendations should be patient specific and based on institutional guidelines

Mechanism of Action for the Drug Class

Magnesium is an important cofactor in many enzymatic reactions in the body involving protein synthesis and carbohydrate metabolism (at least 300 enzymatic reactions require magnesium). Magnesium maintains normal nerve and muscle function, energy production, nutrient metabolism, and bone and cell formation. Magnesium oxide is a common oral magnesium supplement utilized for the treatment and prevention of hypomagnesemia.

Members of the Drug Class

In this section: magnesium oxide
Others: magnesium hydroxide, magnesium chloride, magnesium citrate, magnesium gluconate, magnesium sulfate

⦿ Magnesium Oxide

Brand Name

Uro-Mag, Maox, Mag-200, Mag-Ox 400

Generic Name

Magnesium oxide

OTC

Dosage Forms

Tablet, capsule

Usage

Treatment and prevention of hypomagnesemia, dietary supplement, relief of acid indigestion and upset stomach; short-term treatment of occasional constipation

Pregnancy Category

Magnesium crosses the placenta; serum concentrations in the fetus are similar to those in the mother

Dosing

- Dosing is listed as: magnesium oxide salt component or amount of elemental magnesium
- 400 mg magnesium oxide = elemental magnesium 240 mg = magnesium 19.9 mEq = magnesium 9.85 mmol
- Antacid (dosage in terms of magnesium oxide salt):
  - Adults:
    - Initial dose: 400–800 mg PO daily or in divided doses
- Prevention and treatment of hypokalemia (dosage in terms of magnesium oxide salt)
  - Adults:
    - Initial dose:
      - Magnesium oxide (Mag–Ox 400) 400–800 mg PO daily or in divided doses, take with food
      - Uro-Mag: 3–4 capsules (420–560 mg) daily with food

Adverse Reactions: Most Common

Diarrhea, hypermagnesemia

Major Drug Interactions

Magnesium Oxide's Effect on Other Drugs

Magnesium preparations have been reported to decrease the pharmacologic effect of many drugs when concomitantly administered. Monitor for therapeutic efficacy and failure.

- Levothyroxine: magnesium salts may decrease the serum concentration of levothyroxine. Separate administration of oral levothyroxine and oral magnesium salts by at least 4 hours
- Fluoroquinolones: Magnesium salts may decrease the serum concentration of fluoroquinolones. Administer oral fluoroquinolones at least 4 hours prior to magnesium
- Bisphosphonates: Magnesium salts may decrease the serum concentration of bisphosphonates. Avoid administration of oral magnesium salts within 2 hours before or after.
- Mycophenolate: Magnesium salts may decrease the serum concentration of mycophenolate. Separate doses of mycophenolate and oral magnesium salts. Monitor for reduced effects of mycophenolate if taken concomitantly with oral magnesium salts.
- Tetracyclines: Magnesium salts may decrease the absorption of tetracyclines.

Contraindications

No known contraindications

Essential Monitoring Parameters

Serum magnesium: 1.5–2.5 mg/dl (Of note: slightly different ranges are reported by different laboratories)

Counseling Points

- Take with food to minimize GI adverse effects
- Separate administration of magnesium by at least 2 hours from other medications

Key Points

- Dosing recommendations should be patient specific and based on patient's magnesium level, concomitant medications, and GI adverse effects
- Magnesium preparations have been reported to decrease the pharmacologic effect of many drugs when concomitantly administered. Separate administration of magnesium by at least 2 hours from other medications. Monitor for therapeutic efficacy and failure.

ANTICHOLINERGICS AND ANTISPASMODICS, OVERACTIVE BLADDER AGENTS

Introduction

Anticholinergic and antispasmodic agents are used to suppress premature detrusor contractions, enhance bladder storage, and relieve urge urinary incontinence symptoms and complications. These agents are recommended as second-line for the treatment of overactive bladder (OAB) after behavioral therapies. The extended-release and topical products are associated with lower rates of anticholinergic side effects than the immediate-release formulations.

Mechanism of Action for the Drug Class

Anticholinergic agents for OAB inhibit the action of acetylcholine on muscarinic receptors in the detrusor smooth muscle of the overactive bladder, resulting in increased bladder capacity, decreased bladder contractions, decreased detrusor muscle pressure, and decreased bladder irritability

Usage for the Drug Class

OAB, neurogenic bladder (oxybutynin only)

Contraindications for the Drug Class

- OAB anticholinergic agents are contraindicated in patients at risk for or with known urinary or gastric retention or uncontrolled angle-closure glaucoma
- Tolterodine and trospium are contraindicated in myasthenia gravis

Counseling Points for the Drug Class

- Drink small sips of water, use OTC saliva replacement therapy, or eat sugarless candy to lessen effects of dry mouth

Key Points for the Drug Class

- OAB anticholinergic agents are included in the American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Use caution in patients over 65 years of age.
- OAB anticholinergic agents cause urinary retention and should be used with caution in patients with bladder outflow obstruction
- Formulation considerations:
  - Immediate-release oral tablets: Increased incidence of adverse drug effects and multiple daily doses
  - Extended-release oral tablets: Decreased risk of xerostomia compared with immediate-release tablets; important to swallow whole
  - Transdermal gel: Risk for application-site reactions; significantly more costly than oral formulations
  - Transdermal patch: risk for application-site reactions; available without a prescription
- Trospium does not readily cross the blood-brain barrier and may have fewer CNS side effects
- When initiating treatment, start with lowest dose and titrate slowly, as tolerated
- An adequate trial is 4 weeks before treatment failure can be determined
- If patients experience intolerable adverse effects or inadequate symptom relief, a trial with another antimuscarinic can be initiated

Members of the Drug Class

In this section: Darifenacin, oxybutynin, tolterodine, solifenacin. Others: Fesoterodine, trospium

◉ Darifenacin

Brand Names

Enablex

Generic Name

Darifenacin

Rx Only

Dosage Form

Tablet

Pregnancy Category C

Dosing

- Extended-release tablet: 7.5 mg once daily; if inadequate response after 2 weeks, may increase to 15 mg once daily
- Renal dosage adjustment: No dosage adjustment necessary
- Hepatic dosage adjustment:
  - Mild impairment (Child-Pugh class A): No dosage adjustment necessary
  - Moderate impairment (Child-Pugh class B): Do not exceed 7.5 mg/day
  - Severe impairment (Child-Pugh class C): Use is not recommended (not studied)
- Dosage adjustment with concomitant potent CYP3A4 inhibitors: Do not exceed 7.5 mg/day

Adverse Reactions: Most Common

Constipation, xerostomia, headache, dyspepsia

Adverse Reactions: Rare/Severe/Important

Anaphylactoid reaction, angioedema, erythema multiforme, granuloma, hallucination

Major Drug Interactions

Drugs Affecting Darifenacin

- Anticholinergic agents: Additive anticholinergic side effects
- CYP3A4 inhibitors: May increase levels
- CYP3A4 inducers: May decrease levels
- Thioridazine: Avoid concomitant use

Darifenacin's Effect on Other Drugs

- Medications metabolized by CYP2D6 that have a narrow therapeutic index: May increase levels

Contraindications

In addition to those listed above:

Essential Monitoring Parameters

Number of micturitions per day, number of incontinence episodes per day, symptoms of urgency, use of absorbent products (at baseline, at 4 weeks, and periodically thereafter)

Counseling Points

- Swallow tablets whole
- May cause constipation, headache, dizziness, and dyspepsia

Key Points

- Anticholinergic side effects are common (xerostomia in 19% to 35% of patients, constipation in 15% to 21% of patients)
- Limit the dose with potent CYP3A4 inhibitors
- Contraindications include urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, and paralytic ileus, GI, or GU obstruction

Oxybutynin

Brand Names

Ditropan, Ditropan XL, Gelnique, Oxytrol

Generic Name

Oxybutynin

Rx and OTC

Rx: Ditropan, Ditropan XL, Gelnique
OTC: Oxytrol

Dosage Forms

Transdermal gel, transdermal patch, oral syrup, oral tablet, oral extended-release tablet

Pregnancy Category B

Dosing

- Adult (OAB)
  - Immediate-release oral tablet: 5 mg, 2 to 3 times daily; maximum: 5 mg, 4 times daily
  - Extended-release oral tablet: Initial dose: 5–10 mg once daily; adjust dose in 5-mg increments at weekly intervals to a maximum of 30 mg once daily
  - 10% transdermal gel: Apply contents of 1 sachet (100 mg/g) to clean, dry, intact skin on the abdomen, upper arms/shoulders, or thighs once daily
  - Transdermal patch: Apply one 3.9 mg/day patch twice weekly (every 3 to 4 days) to clean, dry, intact skin on abdomen, hip, or buttocks
- Geriatric (OAB)
  - Immediate-release oral tablet: Initial dose: 2.5 mg, 2 to 3 times daily; increase cautiously; use with caution in patients > 65 years of age
- Pediatric (OAB/neurogenic bladder)
  - Immediate-release oral tablet:
    - Children ≥ 5 years of age and adolescents: 5 mg twice daily; maximum: 5 mg 3 times daily
  - Extended-release oral tablet:
    - Children ≥ 6 years of age and adolescents: 5 mg once daily; adjust dose as needed in 5 mg increments at weekly intervals to a maximum dose of 20 mg once daily
- Renal dosage adjustment: No dosage adjustment provided in manufacturer's labeling (not studied)
- Hepatic dosage adjustment: No dosage adjustment provided in manufacturer's labeling (not studied)

Adverse Reactions: Most Common

- Oral formulations: Xerostomia, xerophthalmia, blurred vision, constipation, nausea, delirium, headache, dizziness, drowsiness, sedation, urinary retention, urinary tract infection
- Transdermal gel formulation: Xerostomia, application-site reaction, including anesthesia, irritation, pain, papules
- Transdermal patch formulation: Xerostomia, constipation, application-site pruritus, erythema, and macules

Adverse Reactions: Rare/Severe/Important

Tachycardia, hallucinations, mydriasis

Major Drug Interactions

Drugs Affecting Oxybutynin

Anticholinergics: Additive anticholinergic side effects

Oxybutynin's Effect on Other Drugs

Prokinetic GI agents, nitroglycerin: Increases levels

Essential Monitoring Parameters

Number of micturitions per day, number of incontinence episodes per day, symptoms of urgency, use of absorbent products (at baseline, at 4 weeks, and periodically thereafter)

Counseling Points

- Common side effects include dry mouth and constipation
- Extended-release tablet: You may see a tablet-like substance in the stool
- Transdermal patch: Apply to clean, dry, intact skin on abdomen, hip, or buttocks. Select a new site for each new patch. Do not apply more than 1 patch at a time. Avoid reapplication to the same site within 7 days. Wash hands thoroughly following application.
- Transdermal gel: Apply to clean, dry, intact skin on abdomen, thighs, or upper arms/shoulders. Rotate sites. Do not apply to the same site on consecutive days. Wash hands thoroughly after use. Cover treated area with clothing after gel has dried to prevent transfer of medication to others. Do not bathe, shower, or swim until 1 hour after gel has been applied.

Key Points

- Exclusions for self-care with OTC transdermal patch include pain or burning when urinating; hematuria; unexplained lower back or side pain; cloudy or foul-smelling urine, males, patients less than 18 years of age, patients with SUI (symptoms include urine loss with coughing, sneezing, or laughing); diagnosis of urinary or gastric retention; glaucoma; or hypersensitivity to oxybutynin
- Rates of xerostomia can be very high, formulation-related, and dose-related (oral: 35% to 71%; transdermal gel: 8% to 12%; transdermal patch: 4% to 10%)
- Contraindications include urinary retention, gastric retention, and uncontrolled narrow-angle glaucoma

◉ Solifenacin

Brand Names

VESIcare

Generic Name

Solifenacin

Rx Only

Dosage Form

Tablet

Pregnancy Category C

Dosing

- Extended-release tablet: 5 mg once daily; if tolerated, may increase to 10 mg once daily
- Renal dosage adjustment: Use with caution in reduced renal function; CrCl < 30 ml/min: Maximum dose of 5 mg/day
- Hepatic dosage adjustment: Use with caution in reduced hepatic function
  - Mild impairment (Child-Pugh class A): No dosage adjustment necessary
  - Moderate impairment (Child-Pugh class B): Do not exceed 5 mg/day
  - Severe impairment (Child-Pugh class C): Use is not recommended (not studied)
- Dosage adjustment with concomitant potent CYP3A4 inhibitors: Do not exceed 5 mg/day

Adverse Reactions: Most Common

Constipation, xerostomia, dyspepsia, urinary tract infection, blurred vision

Adverse Reactions: Rare/Severe/Important

Anaphylactoid reaction, angioedema, atrial fibrillation, hallucination, prolonged Q-T interval, renal or hepatic toxicity

Major Drug Interactions

Drugs Affecting Solifenacin

- Anticholinergic agents: Additive anticholinergic side effects
- CYP3A4 inhibitors: May increase levels
- CYP3A4 inducers: May decrease levels

Solifenacin's Effect on Other Drugs

- Cannabinoid-containing products, QTc-prolonging agents, thiazide, and thiazide-like diuretics: Increases levels or effect

Essential Monitoring Parameters

Number of micturitions per day, number of incontinence episodes per day, symptoms of urgency, use of absorbent products (at baseline, at 4 weeks, and periodically thereafter)

Counseling Points

- Swallow tablets whole
- May cause constipation, dry mouth, dyspepsia, urinary tract infection, and blurred vision
- Stop using solifenacin and report to your healthcare team if you experience severe dizziness, severe loss of strength, difficulty in breathing, confusion,

hallucinations, severe abdominal pain or constipation, lack of sweat, or irregular heartbeat

Key Points

- Anticholinergic side effects are common and dose related (xerostomia in 11% to 28% of patients, constipation in 5% to 13% of patients)
- Limit the dose with potent CYP3A4 inhibitors
- Contraindications include urinary retention, gastric retention, and uncontrolled narrow-angle glaucoma

Tolterodine

Brand Names

Detrol, Detrol LA

Generic Name

Tolterodine

Dosage Forms

Tablet, capsule, extended-release capsule

Pregnancy Category C

Dosing

- Extended-release capsule:
  - 4 mg once daily, may reduce to 2 mg/day based on individual response and tolerability
  - Renal dosage adjustment:
    - CrCl = 10–30 ml/min: 2 mg once daily
    - CrCl < 10 ml/min: Use is not recommended (not studied)
  - Hepatic dosage adjustment:
    - Mild-to-moderate hepatic impairment (Child-Pugh class A or B): 2 mg once daily
    - Severe hepatic impairment (Child-Pugh class C): Use is not recommended (not studied)
  - Dosage adjustment with concomitant potent CYP3A4 inhibitors: 2 mg once daily
- Immediate-release tablet:
  - 2 mg twice daily; may reduce to 1 mg twice daily based on individual response and tolerability
  - Renal dosage adjustment: CrCl 10–30 ml/min: Reduce dose to 1 mg twice daily; use with caution
  - Hepatic dosage adjustment: Reduce dose to 1 mg twice daily; use with caution
  - Dosage adjustment with potent CYP3A4 inhibitors: Reduce dose to 1 mg twice daily

Adverse Reactions: Most Common

Constipation, xerostomia, abdominal pain, diarrhea, dyspepsia, headache, dizziness

Adverse Reactions: Rare/Severe/Important

Anaphylactoid reaction, dementia, memory impairment, hallucination, memory impairment, palpitations, prolonged Q-T interval, angioedema

Major Drug Interactions

Drugs Affecting Tolterodine

- Anticholinergic agents: Additive anticholinergic side effects
- CYP3A4 and CYP2D6 inhibitors: Increase anticholinergic side effects
- CYP3A4 and CYP2D6 inducers: Increase metabolism

Tolterodine's Effect on Other Drugs

- Warfarin: May increase effects

Essential Monitoring Parameters

- Number of micturitions per day, number of incontinence episodes per day, symptoms of urgency, use of absorbent products (at baseline, at 4 weeks, and periodically thereafter)
- INR in patients receiving concomitant warfarin therapy
- Renal function (BUN, creatinine)
- Hepatic function

Counseling Points

- Do not crush, chew, or open extended-release capsules
- Exercise caution with driving because this medication may cause sedation
- Do not take if you are allergic to fesoterodine

Key Points

- Anticholinergic side effects are common and dose related (xerostomia in 11% to 28% of patients, constipation in 5% to 13% of patients)
- Tolterodine is a major substrate of CYP3A4 and CYP2D6
- Limit the dose with potent CYP3A4 inhibitors
- Contraindications include urinary retention, gastric retention, and uncontrolled narrow-angle glaucoma

BETA$_3$ AGONIST, OVERACTIVE BLADDER AGENT

Introduction

In clinical trials, mirabegron reduced urgency episodes and the number of both micturition and incontinence episodes per 24 hours. Additionally, mirabegron increased the volume of urine voided per micturition and was generally associated with improvement in health-related quality of life and treatment satisfaction. It is generally well tolerated and carries a smaller risk of anticholinergic side effects compared with traditional antimuscarinic agents used in the treatment of OAB.

Mechanism of Action for the Drug Class

Beta$_3$ agonists selectively activate beta$_3$ adrenergic receptors in the bladder, causing a relaxation of the detrusor smooth muscle during the urine storage phase and increasing bladder capacity.

Members of the Drug Class

In this section: Mirabegron. Others: None

◉ Mirabegron

Brand Name

Myrbetriq

Generic Name

Mirabegron

Rx Only

Dosage Form

Tablet

Usage

OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency

Pregnancy Category C

Dosing

- OAB: Initial: 25 mg once daily. May increase after 8 weeks to 50 mg once daily based on efficacy and tolerability.
- Renal dosage adjustment:
  - CrCl 30–89 ml/min: No dosage adjustment necessary
  - CrCl 15–29 ml/min: Do not exceed 25 mg once daily
  - CrCl <15 ml/min: Not recommended (not studied)
  - Hemodialysis: Not recommended (not studied)
- Hepatic dosage adjustment:
  - Mild impairment (Child-Pugh class A): No dosage adjustment necessary
  - Moderate impairment (Child-Pugh class B): Do not exceed 25 mg once daily
  - Severe impairment (Child-Pugh class C): Not recommended (not studied)

Adverse Reactions: Most Common

Hypertension, nasopharyngitis, urinary tract infection, headache

Adverse Reactions for the Drug Class: Rare/Severe/Important

Atrial fibrillation, prostate cancer

Major Drug Interactions for the Drug Class

Drugs Affecting Mirabegron

- Anticholinergic agents, ketoconazole, rifampin, and mifepristone: May increase levels of mirabegron

Mirabegron's Effect on Other Drugs

- Metoprolol and desipramine: The systemic exposure of drugs metabolized by CYP2D5 may be increased; when co-administered with mirabegron, a moderate CYP2D6 inhibitor
- Thioridazine, flecainide, propafenone: The systemic exposure may be increased when co-administered with mirabegron, a moderate CYP2D6 inhibitor; monitor closely for toxicity and need for dose adjustment with these narrow therapeutic index CYP2D6 substrates
- Digoxin: Increases plasma concentrations; when co-administered with mirabegron, initiate digoxin at the lowest dose and monitor closely when titrating
- Warfarin: May increase plasma concentrations, monitor INR closely

Essential Monitoring Parameters

- Blood pressure at baseline and periodically thereafter
- Number of micturitions per day, number of incontinence episodes per day, symptoms of urgency, use of absorbent products (at baseline, at 8 weeks, and periodically thereafter)

Counseling Points

- Mirabegron may cause your blood pressure to increase. If you check your blood pressure at home, report large increases in blood pressure to your healthcare team.
- Mirabegron may increase your chances of not being able to empty your bladder if you have bladder outlet obstruction or if you are taking other medications to treat overactive bladder. Tell your healthcare team immediately if you are unable to empty your bladder.

Key Points

- Mirabegron is associated with an increase in blood pressure and is not recommended for use in patients with severe uncontrolled hypertension, defined as systolic blood pressure greater than or equal to 180 mmHg and/or diastolic blood pressure greater than or equal to 110 mmHg.
- Use with caution in patients with bladder outlet obstruction and in patients taking antimuscarinic medications for the treatment of OAB, as it may cause urinary retention
- Mirabegron is a moderate CYP2D6 inhibitor and may increase the systemic exposure to CYP2D6 substrates, such as metoprolol and desipramine. Monitor for toxicities and the need for dosage adjustment, especially in patients taking narrow therapeutic index CYP2D6 substrates, including thioridazine, flecainide, and propafenone.

PHOSPHODIESTERASE INHIBITORS, ERECTILE DYSFUNCTION AGENTS

Introduction

Phosphodiesterase inhibitors are used as first-line treatment of erectile dysfunction. They have a convenient route of administration, low incidence of side effects, and are effective.

Mechanism of Action for the Drug Class

The agents in this class inhibit phosphodiesterase 5 (PDE5), leading to increased levels of cyclic guanosine monophosphate and enhancing smooth muscle relaxation in the corpus cavernosum of the penis and smooth muscle of the pulmonary vasculature. Overall, these agents enhance the nitric oxide–induced relaxation of penile vascular smooth muscle. Some have complex dosing schedule adjustments for renal and hepatic impairment as well as concurrent medications.

Usage for the Drug Class

Treatment of erectile dysfunction, pulmonary arterial hypertension, benign prostatic hyperplasia (BPH)

Adverse Reactions for the Drug Class: Most Common

Headache, flushing, dizziness, rhinitis, visual abnormalities (inability to distinguish between blue and green)

Adverse Reactions for the Drug Class: Rare/Severe/Important

Chest pain, myocardial infarction, prolonged QT interval, seizure, optic neuropathy, decreased hearing, sudden hearing loss, priapism

Major Drug Interactions for the Drug Class

Drugs Affecting Phosphodiesterase Inhibitors

- Potent CYP3A4 inhibitors (i.e., protease inhibitors, erythromycin, azole antifungals): Increase levels
- Nitrates: Potentiate vasodilation, potentially causing fatal hypotension
- Antihypertensives: Potentiate antihypertensive effect

Contraindication for the Drug Class

Concomitant use of organic nitrates of any kind

Counseling Points for the Drug Class

- PDE5 inhibitors offer no protection against sexually transmitted infections
- These agents are ineffective in the absence of sexual arousal
- Do not take if you are using any form of nitrate
- Be aware of signs of low blood pressure, such as dizziness and unsteadiness
- Report sudden decrease or loss of hearing or vision
- Priapism (prolonged erection > 6 hours) is a medical emergency. Seek immediate medical attention.
- Do not engage in sexual activity if clinically inadvisable

Key Point for the Drug Class

Nitrates are contraindicated while using phosphodiesterase inhibitors

Members of the Drug Class

In this section: Sildenafil, tadalafil, vardenafil. Other: Avanafil

Sildenafil

Brand Names

Viagra, Revatio

Generic Name

Sildenafil

Usage

Treatment of erectile dysfunction, pulmonary arterial hypertension

Pregnancy Category B

Dosage Form

Tablet, oral suspension, intravenous solution

Dosing

- Erectile dysfunction: 50 mg 1 hour before anticipated sexual activity; may increase to 100 mg or decrease to 25 mg
- Renal dosage adjustment: If CrCl < 30 ml/min, consider initial dose of 25 mg

- Hepatic dosage adjustment: If mild to moderate impairment (Child-Pugh class A or B), consider starting dose of 25 mg
- Concomitant use of potent CYP3A4 inhibitors: Initial dose of 25 mg
- Concomitant alpha-blocker dose adjustment: Initial dose of 25 mg
- Concomitant protease inhibitors: Maximum dose 25 mg every 48 hours
- Pulmonary arterial hypertension (Revatio only):
  - Oral: 5 mg or 20 mg 3 times daily
  - Intravenous: 2.5 mg or 10 mg 3 times daily

Tadalafil

Brand Names

Cialis, Adcirca

Generic Name

Tadalafil

Usage

Treatment of erectile dysfunction, pulmonary arterial hypertension, BPH

Pregnancy Category B

Dosage Form

Tablet

Dosing

- Erectile dysfunction:
  - As-needed dosing: 10 mg at least 30 minutes before anticipated sexual activity (range 5–20 mg)
  - Once-daily dosing: 2.5 mg taken at the same time daily; may increase to 5 mg/day
  - Renal dosage adjustment:
    - As-needed dosing: If CrCl 30–50 ml/min, then initial dose is 5 mg. If CrCl < 30 ml/min: Maximum dose is 5 mg in 72 hours
    - Once-daily dosing: If CrCl < 30 ml/min, then use is not recommended
  - Hepatic dosage adjustment:
    - As-needed dosing:
      - Mild to moderate impairment (Child-Pugh class A or B): 10 mg maximum dose
      - Severe hepatic impairment (Child-Pugh class C): Use not recommended
  - Dosage adjustment with concomitant potent CYP3A4 inhibitors:
    - As-needed dosing: 10 mg maximum dose in a 72-hour period
    - Once-daily dosing: 2.5 mg/day maximum dose
- Pulmonary arterial hypertension (Adcirca only):
  - 40 mg daily
  - Renal dosage adjustment:
    - CrCl 31–80 ml/min: Initial dose 20 mg once daily. Increase to 40 mg as tolerated
    - CrCl < 31 ml/min: Use is not recommended
  - Hepatic dosage adjustment:
    - Mild to moderate hepatic impairment (Child-Pugh class A or B): Use with caution. Initial dose: 20 mg daily.
    - Severe hepatic impairment (Child-Pugh class C): Avoid use
- BPH:
  - 5 mg once daily
  - Renal dosage adjustment:
    - CrCl = 30–50 ml/min: Initial dose is 2.5 mg once daily. Maximum dose 5 mg daily.
    - CrCl < 30 ml/min: Use not recommended
  - Hepatic dosage adjustment:
    - Mild to moderate hepatic impairment (Child-Pugh class A or B): Maximum dose 10 mg daily. Use with caution.
    - Severe hepatic impairment (Child-Pugh class C): Avoid use
- Not recommended for use in combination with alpha blockers
- Concomitant CYP3A4 inhibitors: Maximum dose 2.5 mg daily

Vardenafil

Brand Names

Levitra, Staxyn

Generic Name

Vardenafil

Usage

Treatment of erectile dysfunction

Pregnancy Category B

Dosage Forms

Tablet, orally disintegrating tablet (ODT)

Dosing

- 10 mg approximately 60 minutes before anticipated sexual activity
- Dosage adjustments: May be increased up to a maximum dose of 20 mg or decreased to 5 mg
- Maximum dosing frequency is once daily
- Renal dosage adjustment: None
- Hepatic dosage adjustment:
  - Mild hepatic impairment: No dosage adjustment needed
  - Moderate hepatic impairment (Child-Pugh class B): Initial dose of 5 mg is recommended; may increase cautiously to maximum of 10 mg
  - Severe hepatic impairment (Child-Pugh class C): Use not recommended
- Dosage adjustment with concomitant potent CYP3A4 inhibitors: Maximum dose of 2.5–5 mg in a 24-hour period, 2.5 mg in 72 hours with ritonavir
- Dosage adjustment with concomitant alpha blockers:
  - Tablet: Initial dose of 5 mg
  - ODT: Do not use to initiate therapy

SMOKING CESSATION AIDS

Introduction

The most commonly used smoking cessation aids in this class are the nicotine replacement agents. These are available in different dosage forms to allow for better compliance based on patients' preferences. Other smoking cessation aids include bupropion and varenicline, which are prescription medications.

Mechanism of Action for Nicotine Replacement Therapy

Nicotine replacement agents provide smaller amounts of nicotine than that found in cigarettes in an effort to prevent or reduce withdrawal symptoms.

Member of the Drug Class

In this section: Nicotine and varenicline
Others: None

◉ Nicotine

Brand Names

Nicorette (gum), Thrive (gum, lozenge), Nicorette Mini (lozenge), Nico-Derm CQ (patch), NICOrelief (gum, lozenge), Nicotine Step 1 (patch), Nicotine Step 2 (patch), Nicotine Step 3 (patch) Nicotrol NS (nasal spray), Nicotrol (inhaler)

Generic Name

Nicotine

Rx and OTC

Rx: Nicotrol NS, Nicotrol Inhaler
OTC: Nicotine gum, nicotine lozenge, nicotine patch

Dosage Forms

Gum, lozenge, patch, nasal spray, oral inhaler

Usage

Smoking cessation aid for the relief of nicotine withdrawal symptoms and cravings

Pregnancy Category D (Rx products)

The use of nicotine replacement products to aid in smoking cessation has not been adequately studied in pregnant women (amount of nicotine exposure is varied). Nonpharmacologic treatments are recommended. If the benefits of nicotine replacement therapy outweigh the unknown risks, it should be done under close supervision.

Dosing

- Tobacco cessation (patients should be advised to completely stop smoking upon initiation of therapy):
- Nicotine Gum:
  - Patients who smoke their first cigarette within 30 minutes of waking should use the 4 mg strength; otherwise, the 2 mg strength is recommended.
  - Maintenance dose (12-week dosing schedule):
    - Weeks 1 to 6: Chew one piece of gum every 1 to 2 hours (maximum: 24 pieces/day); to increase chances of quitting, chew at least nine pieces/day during the first 6 weeks
    - Weeks 7 to 9: Chew one piece of gum every 2 to 4 hours (maximum: 24 pieces/day)
    - Weeks 10 to 12: Chew one piece of gum every 4 to 8 hours (maximum: 24 pieces/day)
- Nicotine Lozenge:
  - Patients who normally smoke within 30 minutes of awakening: 4 mg strength
  - Patients who normally smoke 30 minutes after awakening in the morning: 2 mg strength
  - Maintenance dose:
    - Weeks 1 to 6: 1 lozenge every 1 to 2 hours (maximum: 5 lozenges every 6 hours; 20 lozenges/day); to increase the chances of quitting, use at least 9 lozenges/day during the first 6 weeks
    - Weeks 7 to 9: 1 lozenge every 2 to 4 hours (maximum: 5 lozenges every 6 hours; 20 lozenges/day)
    - Weeks 10 to 12: 1 lozenge every 4 to 8 hours (maximum: 5 lozenges every 6 hours; 20 lozenges/day)
- Nicotine Transdermal Patch (Topical):
  - Adjustment may be required during initial treatment (move to higher dose if experiencing withdrawal symptoms; lower dose if side effects are experienced).
  - > 10 cigarettes/day: Begin with 21 mg/day patch applied daily for 6 weeks, followed by 14 mg/day patch applied daily for 2 weeks, followed by 7 mg/day patch applied daily for 2 weeks, then discontinue
  - ≤ 10 cigarettes/day: Begin with 14 mg/day patch applied daily for 6 weeks, followed by 7 mg/day patch applied daily for 2 weeks, then discontinue
- Nicotrol nasal spray (NS):
  - Each dose (two sprays; one spray in each nostril) contains 1 mg of nicotine)
  - Initial dose: 1–2 doses (2–4 sprays)/hour
  - Maintenance dose: Individualized for a duration of 3 months; For best results, use at least the recommended minimum of 8 doses per day (less is unlikely to be effective)
  - Maximum dose: 5 mg (5 doses or 10 sprays)/ hour, 40 mg (40 doses or 80 sprays)/day
- Nicotrol Inhaler:
  - Initial dose: 6–16 cartridges daily for up to 12 weeks; best effect is achieved by frequent continuous puffing (20 minutes)

- Maintenance dose: Individualized for 12 weeks, then tapered gradually over an additional 6 to 12 weeks
- Maximum dose: 16 cartridges/day for 12 weeks before tapering

Adverse Reactions: Most Common

- Palpitations, tachycardia, insomnia, headache, hypertension
- Gum and lozenge: Mouth soreness, throat irritation, dyspepsia, nausea, gingivitis, taste perversion, headache
- Transdermal patch: Local skin reaction (skin), insomnia, vivid dreams
- Nicotrol NS: Nasal irritation, headache
- Nicotine Inhaler: Local irritation of mouth and throat, headache

Major Drug Interactions

Drugs Affecting Nicotine

- Cimetidine: May increase serum concentration.
- Varenicline: May enhance the adverse/toxic effect of nicotine

Essential Monitoring Parameters

Signs and symptoms of nicotine toxicity (e.g., severe headache, dizziness, mental confusion, disturbed hearing and vision, abdominal pain; rapid, weak and irregular pulse; salivation, nausea, vomiting, diarrhea, cold sweat, weakness), effectiveness of nicotine replacement therapy (e.g. amount of "quit" days), and occurrence of adverse effects of individual nicotine replacement therapy

Contraindications

Patients immediately postmyocardial infarction, life-threatening arrhythmias, worsening or unstable angina

Counseling Points

- Nicotine gum:
  - Start on quit date
  - Chew gum slowly until a tingling sensation or "peppery taste" occurs, then "park" between the gum and the cheek. When tingling subsides, chew again until tingling returns. Repeat process until most of the tingling sensation is gone (~30 minutes).
  - Avoid eating or drinking 15 minutes before chewing gum and while gum is in mouth
  - Do not use nicotine gum if you have dental problems
- Nicotine lozenge:
  - Start on quit date
  - Avoid eating or drinking 15 minutes before and while using the lozenge
  - Suck on the lozenge and move it from side to side; suck each piece until it dissolves
  - Do not chew or swallow the lozenge. Minimize swallowing while dissolving the lozenge.
- Nicotine patch:
  - Start on quit date
  - Apply new patch every 24 hours to clean, hairless, dry skin without cuts or scratches on upper body; rotate sites
  - Wash site of application with water only; soap will increase absorption
  - Dispose of patches and gum carefully and out of reach of children and pets
  - If sleep disruption or vivid dreams occur, remove at night before bedtime and apply a new patch upon awakening
  - Do not smoke when using the patch
- Nicotrol NS:
  - Start on quit date
  - Tilt head back slightly; do not sniff, inhale through nose, or swallow while spraying
- Nicotrol Inhaler:
  - Start on quit date
  - Inhale like smoking a cigarette
  - Avoid eating or drinking 15 minutes before and during use

Key Points

- Use with caution in patients with GI ulcers because nicotine may delay healing
- Avoid use in patients immediately postmyocardial infarction, with life-threatening arrhythmias, and/or with worsening or unstable angina
- Nicotrol NS: Not recommended for patients with chronic nasal disorders (e.g., sinusitis, nasal polyps, and allergic rhinitis) because nasal mucosa irritation can occur. Avoid use in severe reactive airway disease.
- Nicotrol inhaler: Avoid use in cases of bronchospastic disease

Varenicline

Brand Name

Chantix

Generic Name

Varenicline

Mechanism of Action

Varenicline is a partial neuronal alpha-4 beta–2 nicotinic receptor agonist, thus producing agonist activity at the nicotinic receptor but at a lower level than nicotine. Varenicline also prevents nicotine from binding to this receptor, preventing stimulation of the central nervous mesolimbic dopamine system, which is responsible for the reinforcement-and-reward experience associated with smoking.

Rx Only

Dosage Form

Tablet

Usage

Treatment of smoking cessation

Pregnancy Category

Adverse events have been observed in animal reproduction studies

Dosing

- Start 1 week before target quit date
  - Initial:
    - Days 1 to 3: 0.5 mg once daily
    - Days 4 to 7: 0.5 mg twice daily
  - Maintenance (≥ Day 8): 1 mg twice daily for 11 weeks; may consider a temporary or permanent dose reduction if usual dose is not tolerated.
- Renal dosage adjustment: If CrCl < 30 ml/min, initiate 0.5 mg once daily to a maximum dose of 0.5 mg twice daily

Adverse Reactions: Most Common

Insomnia, vivid dreams, irritability, constipation, flatulence, nausea (dose dependent), vomiting, headache

Adverse Reaction: Rare/Severe/Important

Abnormal behavior, changes in mood, suicidal ideation, hypersensitivity reactions (Stevens-Johnson syndrome, angioedema), chest pain, myocardial infarction

Major Drug Interactions

Drugs Affecting Varenicline

- Alcohol may increase the risk of adverse psychiatric events
- H2-antagonists (i.e., cimetidine) may increase serum concentrations, especially in patients with severe renal impairment
- Quinolone antibiotics (i.e., levofloxacin) may increase serum concentrations, especially in patients with severe renal impairment
- Trimethoprim may increase serum concentrations, especially in patients with severe renal impairment

Varenicline's Effect on Other Drugs:

- Nicotine: Varenicline may enhance the adverse/toxic effect of nicotine
- Alcohol (Ethyl): Varenicline may enhance the adverse/toxic effect of alcohol as tolerance may be decreased

Contraindications

Specific contraindications have not been established

Essential Monitoring Parameters

Monitor for behavioral changes and psychiatric symptoms (e.g., agitation, depression, suicidal behavior, suicidal ideation), effectiveness of varenicline therapy (e.g. amount of "quit" days), and occurrence of adverse effects

Counseling Points

- Start medication 1 week before quit date
- Report changes in mood (e.g., depression, suicide ideation, emotional/behavioral changes) to your healthcare provider
- Take with food to reduce nausea
- Take evening dose with dinner instead of at bedtime if insomnia occurs

Key Point

Use with caution in patients with cardiovascular disease

URINARY ANALGESICS

Introduction

The urinary analgesic phenazopyridine is an azo dye that has analgesic or local anesthetic action on the urinary tract mucosa. It is used short-term to ease symptoms of urinary tract infections (UTIs).

Mechanism of Action for the Drug Class

The azo dye exerts local anesthetic or analgesic action on the urinary tract mucosa through an unknown mechanism.

Members of the Drug Class

In this section: Phenazopyridine
Others: None

Phenazopyridine

Brand Names

Pyridium, Azo, Baridium, Urinary Pain Relief, Uristat

Generic Name

Phenazopyridine

Rx and OTC

Rx: Pyridium
OTC: Azo, Baridium, Urinary Pain Relief, Uristat

Dosage Form

Tablet

Usage

Dysuria, symptomatic relief of pain, burning, frequency, and urgency associated with irritation of the lower urinary tract mucosa caused by infection, trauma, surgery, endoscopic procedures, or the passage of sounds or catheters

Pregnancy Category B

Dosing

- Adults:
  - OTC: 190 mg 3 times daily with or after meals for up to 2 days. Should not be used for more than 2 days when used for self-medication or concomitantly with an antibiotic.
  - Rx: 200 mg 3 times daily after meals for 2 days when used concomitantly with an antibiotic
- Children ≥ 12 years of age:
  - Manufacturer's labeling: refer to adult dosing
  - Alternative dosing: 12 mg/kg in 3 divided doses/day given after meals. Recommended duration of therapy is as follows:
    - Duration of therapy (adults and children ≥ 12 years of age)
      - Relief of irritation due to trauma, surgery, endoscopic procedures, or passage of sounds or catheters: Discontinue when pain and discomfort are relieved, usually after 3 to 15 days
      - Relief of irritation due to infection: Use in combination with an anti-infective agent. After 2 days of dual therapy, discontinue use of phenazopyridine and continue anti-infective agent monotherapy for full course of therapy.
- Renal dosage adjustment:
  - CrCl = 50–80 ml/min: Change dosing interval to every 8–16 hours
  - CrCl <50 ml/min: Contraindicated in renal impairment
- Hepatic dosage adjustment: Contraindicated in severe hepatic impairment

Adverse Reactions: Most Common

Headache, pruritus, abdominal cramps

Adverse Reactions: Rare/Severe/Important

Hemolytic anemia, hepatotoxicity, nephrotoxicity, methemoglobinemia

Major Drug Interactions

Drugs Affecting Phenazopyridine

Dapsone (topical), nitric oxide, tetracaine (topical): Increases serum levels, which may increase the likelihood and the toxic effect of methemoglobinemia.

Phenazopyridine's Effect On Other Drugs

Prilocaine, sodium nitrate: Increases serum levels, which may increase the likelihood and the toxic effect of methemoglobinemia

Contraindications

Impaired renal function, glomerulonephritis, uremia, severe hepatic disease, pyelonephritis during pregnancy

Essential Monitoring Parameters

Relief of symptoms, including pain, burning, itching, frequency, and urgency associated with irritation of the lower urinary tract mucosa caused by infection, trauma, surgery, endoscopic procedures, or the passage of sounds or catheters

Counseling Points

- Take with food to decrease stomach upset
- Phenazopyridine may cause an orange-red discoloration of urine and a yellowing of the white portion of eye, leading to staining of contact lenses and undergarments. Tablets may also stain clothing. Stop using phenazopyridine if eyes or skin become discolored.
- Stop using phenazopyridine and contact your healthcare team if you experience blue or gray discoloration of the lips, nails, or skin; irregular heartbeats, seizures, severe dizziness, shortness of breath, severe loss of strength, or vision changes

Key Points

- Phenazopyridine is only effective for relief of symptoms and use should not delay definitive diagnosis and treatment of the source of discomfort
- Phenazopyridine is not a substitute for antibiotic therapy or surgery, when indicated
- Phenazopyridine will discolor urine and can interfere with urine dipstick tests to diagnose UTIs
- Discoloration of sclera or skin may indicate accumulation due to impaired renal excretion; discontinuation is recommended.
- The risk for methemoglobinemia is increased for patients receiving concomitant therapy with dapsone (topical), nitric oxide, tetracaine (topical), prilocaine, and sodium nitrate. Monitor patients for signs of methemoglobinemia (hypoxia, cyanosis) when used concomitantly.
- Use with caution in patients with G6PD deficiency, as hemolytic anemia may occur with chronic overdose
- Taking phenazopyridine with food can minimize GI irritation

ANDROGEN

Introduction

Testosterone is a naturally occurring steroid hormone and a medication used to treat male hypogonadism and certain types of breast cancer. Male hypogonadism is a clinical syndrome resulting from insufficient testosterone secretion and has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's syndrome or Leydig cell aplasia. Secondary hypogonadism is the failure of the hypothalamus or pituitary to produce sufficient gonadotropins (FSH, LH).

Mechanism of Action for the Drug Class

Testosterone is the primary endogenous androgen responsible for promoting the growth and development of the male sex organs and maintaining secondary sex characteristics in androgen-deficient males. These effects include the growth and maturation of prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; alterations in body musculature and fat distribution.

Members of the Drug Class

In this section: testosterone gel

Others: testosterone nasal gel, testosterone transdermal cream, testosterone transdermal ointment, testosterone transdermal solution, testosterone transdermal patch, testosterone pellet implant, testosterone intramuscular solution, testosterone buccal, danazol, fluoxymesterone, methyltestosterone, oxandrolone

⦿ Testosterone

Brand Name

AndroGel, AndroGel Pump, Fortesta, Testim, Vogelxo, Vogelxo Pump

Generic Name

Testosterone

Rx Only

Dosage Form

Transdermal gel

Usage

Hypogonadotropic hypogonadism (congenital or acquired), *primary hypogonadism* (congenital or acquired)

Pregnancy Category X

Dosing

- Hypogonadotropic or primary hypogonadism in males
  - AndroGel 1%:
    - 50 mg applied once daily in the morning to the shoulder and upper arms, or abdomen
    - Adjust dose based on testosterone levels
      - Less than normal range: Increase dose from 50–75 mg or from 75–100 mg once daily
      - Greater than normal range: Decrease dose. Discontinue if consistently above normal range when using a 50 mg daily dose
    - Dosage range: 50–100 mg daily
  - AndroGel 1.62%:
    - 40.5 mg applied once daily in the morning to the shoulder and upper arms
    - Adjust dose based on testosterone levels
      - > 750 ng/dl: Decrease dose from 50–75 mg or from 75–100 mg once daily
      - 350–750 ng/dl: Maintain current dose
      - < 350–750 ng/dl: Increase dose by 20.25 mg daily
    - Dosage range: 20.25–81 mg daily
    - Maximum Dosage: 81 mg daily
  - Fortesta:
    - 40 mg applied once daily in the morning to the thighs
    - Adjust dose based on serum testosterone levels
      - ≥ 2500 ng/dl: Decrease dose by 20 mg daily
      - 1250 – < 2500 ng/dl: Decrease dose by 10 mg daily
      - 500 – < 1250 ng/dl: Maintain current dose
      - < 500 ng/dl: Increase dose by 10 mg daily
    - Dosage range: 10–70 mg daily
    - Maximum dosage: 70 mg daily
  - Testim:
    - 50 mg applied once daily in the morning to the shoulder and upper arms
    - Adjust dose based on testosterone levels
      - Less than the normal range: May increase dose from 50–100 mg once daily
    - Maximum dosage: 100 mg daily
  - Vogelxo:
    - 50 mg applied once daily to the shoulder and/or upper arms
    - Adjust dose based on testosterone levels
      - Less than normal range: Increase dose from 50 to 100 mg once daily
    - Maximum dosage: 100 mg daily
- Renal dosage adjustment:
  - No dosage adjustments provided in manufacturer's labeling (not studied)
- Hepatic dosage adjustment:
  - No dosage adjustments provided in manufacturer's labeling (not studied)

Adverse Reactions: Most Common

Increase in PSA, emotional lability (mood swings, affective disorder, impatience, anger, and aggression), hypertension, increased hematocrit or hemoglobin, contact dermatitis

Adverse Reactions: Rare/Severe/Important

Serious abuse-related adverse reactions: cardiac arrest, MI, hypertrophic cardiomyopathy, CHF, CVA, hepatotoxicity, serious psychiatric manifestations (major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility, aggression)

Major Drug Interactions

Drugs Affecting Testosterone

- Adrenocorticotrophic hormone or corticosteroids: Additive fluid retention; use with caution in patients with cardiac, renal, or hepatic disease
- Dehydroepiandrosterone: May increase effects

Testosterone's Effect on Other Drugs

- Blood glucose lowering agents: May increase effects; monitor blood glucose and adjust insulin therapy
- Cyclosporine (systemic): May increase effects
- Warfarin: May increase effects; closely monitor INR and PT

Contraindications

- Men with carcinoma of the breast
- Men with known or suspected carcinoma of the prostate
- Women who are or may become pregnant or who are breastfeeding

Essential Monitoring Parameters

- Prior to initiation of therapy: Morning serum testosterone on 2 separate days
  - AndroGel 1%: Morning serum testosterone levels ~14 days after start of therapy or dose adjustments
  - AndroGel 1.62%: Morning serum testosterone levels 14 and 28 days after starting therapy or dose adjustments and periodically thereafter
  - Fortesta: Serum testosterone levels can be measured 2 hours after application and 14 and 35 days after starting therapy or dose adjustments
  - Testim: Morning serum testosterone levels ~14 days after start of therapy or dose adjustments
  - Vogelxo: Morning serum testosterone levels ~14 days after initiation of therapy (measure prior to application)
- Response to treatment, serum testosterone, adverse events 3 to 6 months following initiation, then annually
- LFTs: 0, 3 to 6 months, then annually
- Hemoglobin and hematocrit: 0, 3 to 6 months, then annually (discontinue if hematocrit > 54%)
- Lipid panel: 0, 3 to 6 months, then annually
- PSA and prostate exam in men > 40 years of age with baseline PSA > 0.6 ng/ml
- Urine and serum calcium levels
- Serum glucose in patients with diabetes

Counseling Points

- Read the medication guide that comes with testosterone before you start taking this medication and each time you get a refill
- Men with known or suspected prostate or breast cancer should not use testosterone products
- Exposure to testosterone in children and women can occur with the use of testosterone gel in men. Signs and symptoms of secondary exposure may include the following:
  - In children: Unexpected sexual development, including inappropriate enlargement of the penis or clitoris, premature development of pubic hair, increased erections, and aggressive behavior
  - In women: Changes in hair distribution, increase in acne, or other signs of testosterone effects
  - The possibility of secondary exposure to testosterone gel should be brought to the attention of a healthcare provider
  - Testosterone products should be promptly discontinued until the cause of the above symptoms is identified
- Strict adherence to the following precautions is advised to minimize the potential for secondary exposure to testosterone:
  - Children and women should avoid contact with unwashed or unclothed application site(s) of men using testosterone gel
  - Patients using testosterone products should apply the product as directed and strictly adhere to the following:
    - Wash hands with soap and water after application
    - Cover the application site(s) with clothing after the gel has dried
    - Wash the application site(s) thoroughly with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated
    - In the event that unwashed or unclothed skin to which AndroGel 1% has been applied comes in contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible
- Testosterone products may lead to side effects, which include:
  - Changes in urinary habits, such as increased urination at night, trouble starting your urine stream, passing urine many times during the day, having an urge that you have to go to the bathroom right away, having a urine accident, being unable to pass urine, and weak urine flow

- Breathing disturbances, including those associated with sleep or excessive daytime sleepiness
- Too frequent or persistent erections of the penis
- Nausea, vomiting, changes in skin color, or ankle swelling

- Testosterone transdermal gel products are alcohol-based and flammable; therefore, avoid fire, flame, or smoking until the gel has dried
- Wait 5 hours before swimming or washing following application of testosterone transdermal gel

Key Points

- Testosterone must be dispensed with the FDA-approved medication guide
- In October 2016, FDA approved class-wide labeling changes for all prescription testosterone products, alerting prescribers to the abuse potential of testosterone and the potential for serious adverse events, especially related to cardiovascular and psychiatric health. Serum testosterone levels may be in the normal or subnormal range in men abusing synthetic testosterone derivatives. Healthcare professionals and patients are encouraged to report adverse events related to the use of testosterone products to the FDA MedWatch Safety Information and Adverse Event Reporting Program.
- In adult men with androgen deficiency syndromes, withhold initial treatment with hematocrit > 50% hyperviscosity, untreated obstructive sleep apnea, uncontrolled severe heart failure, or severe, untreated BPH with International Prostate Symptom Score > 19. Discontinue therapy with hematocrit > 54%.
- Testosterone products may decrease thyroxine-binding globulin, resulting in a reduction in total T_4 and increased resin uptake of T_3 and T_4; free thyroid hormone levels are not impacted
- Patients with BPH who are treated with androgens are at increased risk for worsening of BPH signs and symptoms
- Patients treated with androgens may be at increased risk for prostate cancer
- Cases of secondary exposure resulting in virilization of children and adult women have been reported during postmarketing surveillance efforts. Children and women should avoid contact with unwashed or unclothed application sites in men using transdermal testosterone products

REVIEW QUESTIONS

1. What is the most appropriate dose of colchicine used to treat an acute gout flare in a patient with normal renal function?
   - **a.** 0.6 mg daily
   - **b.** 0.6 mg twice daily
   - **c.** 1.2 mg once, followed by 0.6 mg 1 hour later
   - **d.** 0.6 mg every 1 hour until symptoms resolve

2. Which of the following represents a common adverse effect of allopurinol and an appropriate management strategy?
   - **a.** Acute gout flare: Discontinue allopurinol therapy
   - **b.** GI upset: Take with food
   - **c.** Hypertension: Decrease salt intake
   - **d.** Urinary retention: Decrease fluid intake

3. Which of the following is true regarding the clinical pharmacology of febuxostat?
   - **a.** Febuxostat lowers uric acid levels by inducing xanthine oxidase
   - **b.** Febuxostat is a purine analog
   - **c.** Oxypurinol is a febuxostat metabolite
   - **d.** Febuxostat blocks the conversion of hypoxanthine to xanthine to uric acid

4. Which of the following oxybutynin dosage forms is associated with the highest incidence of xerostomia?
   - **a.** Immediate-release oral tablet
   - **b.** Extended-release oral tablet
   - **c.** Transdermal gel
   - **d.** Transdermal patch

5. Which of the following is a contraindication of darifenacin?
   - **a.** Severe, uncontrolled hypertension
   - **b.** GI obstruction
   - **c.** Concomitant therapy with CYP3A4 inhibitors
   - **d.** Open-angle glaucoma

6. Which of the following is an appropriate counseling point for solifenacin?
   - **a.** Swallow tablets whole
   - **b.** Take with food to minimize diarrhea
   - **c.** Drink at least 3 liters of fluid per day to prevent dry mouth
   - **d.** Take on an empty stomach for maximum absorption

7. Which of the following is a side effect of tolterodine?
   a. Weight loss
   b. Hypersalivation
   c. Constipation
   d. Bladder outlet obstruction

8. A 73-year-old woman has a past medical history of hypertension, osteoarthritis, gout, and depression. Which of the following may be exacerbated by the initiation of mirabegron and requires close monitoring?
   a. Hypertension
   b. Osteoarthritis
   c. Gout
   d. Depression

9. Which of the following is an appropriate counseling point for scopolamine?
   a. Remove the patch before showering
   b. The patch may be applied to the abdomen, upper arm, or buttocks
   c. To prevent motion sickness, apply the patch at least 4 hours prior to exposure
   d. If one patch does not provide enough symptom relief, a second patch can be applied

10. Which of the following is an important monitoring parameter for hydroxychloroquine?
   a. Ophthalmic examinations
   b. Renal function
   c. Serum hydroxychloroquine levels
   d. QTc interval

11. Which of the following medications antagonizes histamine$_1$ receptors, blocks conduction of middle ear vestibular pathways, and results in the reduction of nausea and vomiting associated with motion sickness?
   a. Avodart
   b. Benadryl
   c. Bonine
   d. Transderm-Scop

12. Which of the following is an appropriate counseling point for phenazopyridine?
   a. Phenazopyridine should not be taken with antibiotics
   b. Take on an empty stomach to improve absorption
   c. Stop taking and call your healthcare team immediately if you notice reddish-orange discoloration of the urine
   d. Stop taking phenazopyridine after 2 days of treatment

13. Which of the following monitoring parameter should be completed prior to initiation and periodically throughout therapy with buprenorphine/naloxone?
   a. LFTs
   b. EKG
   c. Urinalysis
   d. CBC

14. In which dosage forms is Narcan supplied?
   a. Sublingual tablet
   b. Sublingual film
   c. Buccal film
   d. Injectable solution

15. Which of the following medications is most likely to interact with testosterone products?
   a. Tamsulosin
   b. Dutasteride
   c. Insulin aspart
   d. Rivaroxaban

16. Which of the following medications is indicated for male-pattern baldness in men?
   a. Propecia
   b. Avodart
   c. Staxyn
   d. Cialis

17. Which of the following is available as a suppository?
   a. Transderm-Scop
   b. Phenergan
   c. Antivert
   d. Cogentin

18. Benztropine is used to treat which of the following conditions?
   a. Drug-induced EPS
   b. Motion sickness
   c. Prevention of nausea and vomiting associated with anesthesia and surgery
   d. Allergy symptoms

19. Which of the following is an appropriate starting dose for tamsulosin?
   a. 0.2 mg daily
   b. 0.4 mg daily
   c. 0.8 mg daily
   d. 1.0 mg daily

20. Which of the following is not a phosphodiesterase inhibitor?
   a. Levitra
   b. Cialis
   c. Flomax
   d. Viagra

21. Concomitant use of benztropine and oxybutynin could cause which of the following?
   a. EPS
   b. Anticholinergic effects
   c. Increased urination
   d. QT prolongation

22. There is a Black Box Warning regarding risk of serious tissue injuries with subcutaneous or intravenous administration of _____.

- **a.** Promethazine
- **b.** Meclizine
- **c.** Sildenafil
- **d.** Isotretinoin

23. Counseling points for vardenafil include all of the following except_____?

- **a.** Vardenafil is ineffective in the absence of sexual arousal
- **b.** Be aware of signs of elevated blood pressure
- **c.** Report sudden loss of vision.
- **d.** Seek immediate medical attending for an erection lasting > 6 hours

24. _____ can cause abnormalities of the external genitalia of a male fetus if the medication is handled by a pregnant woman.

- **a.** Levitra
- **b.** Cialis
- **c.** Flomax
- **d.** Avodart

25. What is an indication for Evzio?

- **a.** Prevention and treatment of motion sickness
- **b.** Treatment and prophylaxis of acute gout attacks
- **c.** Erectile dysfunction
- **d.** Opioid overdose

26. A contraindication to flumazenil is:

- **a.** Tricyclic antidepressant overdose
- **b.** Benzodiazepine overdose
- **c.** Opioid overdose
- **d.** Acetaminophen overdose

27. Which of the following is *not* a counseling point for the oral formulation of potassium chloride?

- **a.** Potassium chloride should be taken with food to minimize GI adverse effects
- **b.** Potassium chloride should be limited to 20–40 mEq/dose to reduce the incidence of GI adverse effects
- **c.** Potassium chloride should be administered at least 2 hours after fluoroquinolones (e.g., ciprofloxacin) as potassium chloride has been reported to decrease the pharmacologic effect of fluoroquinolones when concomitantly administered
- **d.** Potassium chloride sustained release and wax matrix formulations should be swallowed whole and not crushed

28. Which of the following is a potential adverse effect of nicotine replacement therapy?

- **a.** Seizures
- **b.** Tachycardia
- **c.** Respiratory depression
- **d.** Visual abnormalities

29. Which of the following is not a counseling point for the nicotine patch?

- **a.** Do not smoke while on the patch
- **b.** Apply a new patch every 24 hours to clean, hairless, dry skin and rotate sites
- **c.** Avoid eating or drinking 15 minutes before applying a new patch
- **d.** If sleep disruption or vivid dreams occur, remove patch at night (before bedtime) and apply a new patch upon awakening

30. Which of the following smoking cessation therapies should patients be counseled to start 1 week prior to their quit date?

- **a.** Varenicline
- **b.** Nicotrol Inhaler
- **c.** Nicotrol nasal spray
- **d.** Nicotine lozenge

CHAPTER 12

Ophthalmic Products

Susan Kent Romann, PharmD, BCGP

PROPER ADMINISTRATION OF OPHTHALMIC PRODUCTS

Administration of Solutions

Proper instillation of all eye solutions, suspensions, and ointments is necessary for optimal efficacy and prevention of superinfection. Refer to the techniques provided here for all ophthalmic solutions, suspensions, and ointments. Follow these recommended procedures for application of ophthalmic *solutions*:

- Wash hands thoroughly before administration
- Tilt head back or lie down and gaze upward
- Place medication in conjunctival sac and close eyes; do not blink
- Apply light finger pressure on lacrimal sac for 1 to 3 minutes following instillation; See description of *nasolacrimal occlusion* (NLO) below
- If more than one type of ophthalmic solution is used, wait at least 5 minutes before administering second agent
- To avoid contamination, do not touch tip of container to eye or any surface
- For most products, remove contact lenses prior to administration and wait 10 minutes after administration to replace lenses

Administration of Suspensions

Recommended procedures for application of ophthalmic *suspensions* are as follows:

- Shake bottle before instillation
- Follow steps for application of ophthalmic solution

Administration of Ointments

These are the recommended procedures for application of ophthalmic *ointments*:

- Wash hands thoroughly before administration
- Hold the ointment tube in your hand for a few minutes to warm ointment and facilitate flow
- When opening tube for the first time, squeeze out and discard the first 0.25 inch of ointment
- Tilt head backward or lie down and gaze upward
- Gently pull down lower lid to form a pouch
- Place 0.25 to 0.5 inch of ointment in sweeping motion inside the lower eyelid
- To avoid contamination, do not touch tip of container to eye or any surface
- Close the eye for 1 or 2 minutes and roll the eyeball in all directions
- If more than one type of ointment is needed, wait at least 10 minutes before administering the second agent
- Vision may be blurry for up to 20 minutes following administration of ophthalmic ointments
- For most products, remove contact lenses prior to administration and wait 10 minutes after administration to replace lenses

Nasolacrimal Occlusion (NLO)

- Close eyes (do not blink) and apply pressure to the point where the eyelids meet the nose (nasolacrimal duct). Hold for 1 to 3 minutes.
- Before opening eyes, wipe unabsorbed drops and tears from the closed lids with a tissue
- This technique is appropriate for ophthalmic solutions and suspensions. Using NLO ensures that an effective dose stays on the eye surface (improved ocular bioavailability) and decreases systemic side effects.

ANTIBIOTICS, OTHER

Introduction

Ophthalmic antibacterial agents are active against a variety of gram-positive and gram-negative organisms. They are generally used to treat ocular infections involving the conjunctiva or cornea, such as conjunctivitis, keratitis, corneal ulcers, and blepharitis. Many different combination preparations are available on the U.S. market, so caution

should be exercised regarding the selected agent, strength, and formulation when prescribing and/or dispensing these products. In addition, the dosage and frequency of administration varies with each agent; individual package labeling is a useful reference for pharmacists and providers. In general, the risk of superinfection is high when using topical ophthalmic antibiotics due to contamination of the container (e.g., dropper, tube). Proper administration technique is an important counseling point to help reduce the incidence of superinfection (see the beginning of this chapter for the proper administration technique for ophthalmic products). Patients being treated for bacterial conjunctivitis, the most common indication, should be advised not to wear contact lenses until the infection is completely resolved. Disposable lenses should be thrown away, and a new pair should be started. Nondisposable lenses should be thoroughly cleaned before reinsertion following an eye infection. Using a new contact lens case also is recommended.

Members of the Drug Class

In this section: Neomycin/polymyxin B sulfate/gramicidin (combination product), erythromycin, tobramycin (in combination). See section on antibiotics, fluoroquinolones, for additional agents.

Others: Multiple mono and combination products are available containing the following antibacterial agents: Chloramphenicol, gentamicin, bacitracin, tetracycline, trimethoprim, sulfisoxazole, sulfacetamide

◉ Neomycin/Polymyxin B Sulfate/Gramicidin

Mechanism of Action

This combination antibiotic product has multiple mechanisms of action. Most commonly described is its ability to interfere with bacterial protein synthesis by binding to 30S ribosomal subunits, resulting in bacterial cell death. Additionally, it also alters the permeability of the bacterial cell membrane, causing leakage of intracellular contents, and, ultimately, cell death.

Brand Name

Neosporin

Generic Name

Neomycin/polymyxin B sulfate/gramicidin

Rx Only

Dosage Form

Solution

Usage

Superficial ophthalmic infections, such as bacterial conjunctivitis and blepharitis due to strains of microorganisms susceptible to the antibiotic

Pregnancy Category C

Dosing

Instill 1 or 2 drops into the affected eye(s) every 4 hours or 2 drops per hour for severe infections for 7 to 10 days

Adverse Reactions: Most Common

Superinfection, transient burning, stinging, irritation upon instillation

Adverse Reactions: Rare/Severe/Important

Sensitivity reaction, which manifests as itching, reddening, irritation, and edema of the conjunctiva and eyelid or failure to heal; decreased vision

Counseling Points

- For ophthalmic use only
- To avoid contamination, do not touch tip of container to eye or any other surface
- Do not wear contact lenses while using this medication and for the duration of ocular infection

Key Points

- Common adverse effects, including stinging, irritation, and burning, are usually transient and not harmful
- Products containing neomycin have been specifically linked to sensitization reactions, which manifest as itching, reddening, and edema of the conjunctiva and eyelid or failure of infection to heal; contact prescriber if these symptoms occur or if infection persists

◉ Erythromycin

Mechanism of Action

Macrolides bind to the 50S subunit of the bacterial ribosome, inhibiting RNA-dependent bacterial protein synthesis

Brand Name

Generic manufacturers

Generic Name

Erythromycin

Rx Only

Dosage Form

Ointment

Usage

Treatment of superficial ocular infections involving the conjunctiva or cornea caused by organisms susceptible to the antibiotic, prophylaxis of ophthalmia neonatorum due to *Neisseria gonorrhoeae*

Pregnancy Category B

Dosing

- Bacterial conjunctivitis: Apply a 0.5-inch ribbon into the conjunctival sac of the affected eye two to six times daily, depending on severity
- Prophylaxis of ophthalmia neonatorum: Apply a 0.5-inch ribbon into the conjunctival sacs of neonates shortly after birth

Adverse Reactions: Most Common

Blurred vision for the first few minutes after instillation, transient minor irritation, and redness upon instillation

Adverse Reactions: Rare/Severe/Important

Decreased vision, hypersensitivity

Counseling Points

- For ophthalmic use only
- To avoid contamination, do not touch tip of container to the eye or to any other surface
- Do not wear contact lenses while using this medication and for the duration of ocular infection

Key Points

- Erythromycin ophthalmic ointment is a first-line agent in treating simple cases of bacterial conjunctivitis
- Ointments often are preferred for children and those who have difficulty administering medications. The ointment commonly stays on the lid and lashes, providing a therapeutic effect, even if the medication is not applied directly to the conjunctiva.
- Erythromycin is recommended for routine use in all neonates for prophylaxis of ophthalmia neonatorum due to *N. gonorrhoeae*. Importantly, infants diagnosed with gonococcal ophthalmia or born to mothers with gonorrhea require treatment with systemic (oral) antibiotics because topical erythromycin alone is inadequate. Topical antibiotics are not necessary when oral erythromycin is used.
- Topical ophthalmic erythromycin it is not effective for the prevention or treatment of neonatal ocular infections caused by *Chlamydia trachomatis*

ANTIBIOTICS, FLUOROQUINOLONES

Introduction

Fluoroquinolones are among the most commonly prescribed ophthalmic antibiotics on the market. This is likely due to their broad spectrum of action against both gram-positive and gram-negative bacteria. They are used for a variety of ophthalmic infections, including bacterial conjunctivitis and corneal ulcers. They are also considered the agents of choice for conjunctivitis in contact lens wearers.

Mechanism of Action for the Drug Class

Fluoroquinolones work by inhibiting the activity of DNA gyrase and topoisomerase IV, enzymes needed for replication of bacterial DNA. Inhibition of bacterial DNA synthesis results in cell death and accounts for the bactericidal action of these agents.

Usage for the Drug Class

Treatment of ocular infections, including bacterial conjunctivitis and corneal ulcers (keratitis), due to strains of microorganisms susceptible to the antibiotic.

Pregnancy Category C for the Drug Class

Adverse Reactions for the Drug Class: Most Common

- Localized discomfort and irritation; transient burning, pain, or stinging; dry eye; itching; redness; tearing; papillary conjunctivitis; taste disturbance
- During the first 7 intensive days of corneal ulcer treatment, a nonharmful white crystalline precipitate commonly forms on the cornea defect; therapy should be continued. The precipitate usually resolves as the regimen is deescalated (ciprofloxacin).

Adverse Reactions for the Drug Class: Rare/Severe/Important

- Prolonged redness, irritation, swelling, pain, or itching; secondary infection; decreased vision; hypersensitivity; keratitis. Prolonged use may result in fungal or bacterial superinfections.

Counseling Points for the Drug Class

- For ophthalmic use only
- To avoid contamination, do not touch the tip of the container to the eye or to any other surface
- Do not wear contact lenses while using this medication and for the duration of the ocular infection

Key Points for the Drug Class

- Bacterial conjunctivitis is usually self-limiting; however, use of topical antibiotics is common to help accelerate resolution, decrease spread, and prevent complications
- With a broad spectrum of activity and efficacy against gram-positive and gram-negative bacteria, fluoroquinolones are often overused, leading to bacterial

resistance, a common concern among clinicians. They are, however, the drug of choice for treatment of corneal ulcers and conjunctivitis in contact lens wearers due to their activity against *P. aeruginosa*.

Members of the Drug Class

In this section: Ciprofloxacin, gatifloxacin, moxifloxacin, ofloxacin
Others: Besifloxacin, levofloxacin

Ciprofloxacin

Brand Name

Ciloxan

Generic Name

Ciprofloxacin

Rx Only

Dosage Forms

Solution, ointment

Dosing

- Corneal ulcers:
  - Day 1: Instill 2 drops into the affected eye(s) every 15 minutes for the first 6 hours and then 2 drops into the affected eye(s) every 30 minutes for the remainder of the day
  - Day 2: Instill 2 drops into the affected eye(s) hourly
  - Days 3 to 14: Instill 2 drops into the affected eye(s) every 4 hours; treatment may be continued > 14 days in some patients
- Bacterial conjunctivitis:
  - Solution:
    - Days 1 to 2: Instill 1 or 2 drops into the affected eye(s) every 2 hours while awake
    - Days 3 to 7: Instill 1 or 2 drops into the affected eye(s) every 4 hours
  - Ointment:
    - Days 1 to 2: Apply a 0.5-inch ribbon into the conjunctival sac three times a day
    - Days 3 to 7: Apply a 0.5-inch ribbon into the conjunctival sac two times a day

Gatifloxacin

Brand Names

Zymaxid

Generic Name

Gatifloxacin

Rx Only

Dosage Form

Solution

Dosing

- Bacterial conjunctivitis:
  - Day 1: Instill 1 drop into the affected eye(s) every 2 hours while awake, up to a maximum of 8 times a day
  - Days 2–7: Instill 1 drop into the affected eye(s) 2 to 4 times a day while awake

Moxifloxacin

Brand Names

Vigamox, Moxeza

Generic Name

Moxifloxacin

Rx Only

Dosage Form

Solution

Dosing

- Bacterial conjunctivitis:
  - Moxifloxacin (Vigamox): Instill 1 drop into the affected eye(s) 3 times a day for 7 days
  - Moxifloxacin (Moxeza): Instill 1 drop into the affected eye(s) twice daily for 7 days

Ofloxacin

Brand Name

Ocuflox

Generic Name

Ofloxacin

Rx Only

Dosage Form

Solution

Dosing

- Bacterial corneal ulcer:
  - Days 1 and 2: Instill 1 to 2 drops into the affected eye(s) every 30 minutes while awake and every 4 to 6 hours during normal sleeping time
  - Days 3: Instill 1 to 2 drops into the affected eye(s) every hour while awake for 4 to 6 additional days
  - Thereafter: Instill 1 to 2 drops into the affected eye(s) 4 times a day until clinical cure
- Bacterial conjunctivitis:
  - Days 1 and 2: Instill 1 to 2 drops into the affected eye(s) every 2 to 4 hours
  - Days 3 to 7: Instill 1 to 2 drops into the affected eye(s) 4 times a day

ANTIGLAUCOMA AGENTS, TOPICAL

Introduction

Glaucoma is the second leading cause of blindness in the world and the leading cause of blindness among African Americans. Of the different types, primary open-angle glaucoma is the most common, accounting for over 90% of all cases. Although glaucoma may occur at normal intraocular pressures (normotensive glaucoma), it is commonly associated with intraocular hypertension, the only modifiable risk factor that has been identified. As a result, the goal of treatment for open-angle glaucoma and ocular hypertension is the lowering of the intraocular pressure (IOP). Multiple classes of agents are used to lower IOP, and patients often will require combination therapy. Adherence is particularly challenging in treating glaucoma; many products are dosed multiple times per day, and elderly patients, who are typically affected, may have difficulty remembering to take their medications or self-administering eye drops. Newer formulations and therapies have the advantage of once-daily dosing; however, these drugs are usually expensive and may not be covered by insurance.

Members of the Drug Class

In this section: Latanoprost, tafluprost, travoprost, timolol, timolol-XE, timolol/brimonidine (combination product)
Others: Multiple mono and combination products are available containing the following antibacterial agents: Bimatoprost, betaxolol, carteolol, levobunolol, metipranolol, brimonidine, apraclonidine, brinzolamide, dorzolamide, phenylephrine, pilocarpine, carbachol, dipivefrin

◉ Latanoprost

Mechanism of Action

Latanoprost is a prostaglandin analog; it effectively reduces IOP by increasing aqueous humor outflow from the eye

Brand Name

Xalatan

Generic Name

Latanoprost

Rx Only

Dosage Form

Solution

Usage

Treatment of elevated IOP in patients with open-angle glaucoma or ocular hypertension

Pregnancy Category C

Dosing

Instill 1 drop into the affected eye(s) once daily in the evening

Adverse Reactions: Most Common

Increased pigmentation of the iris, eyelash changes, eyelid skin darkening, transient burning and stinging upon instillation, foreign body sensation, blurred vision, conjunctival hyperemia

Adverse Reactions: Rare/Severe/Important

Excessive tearing, eyelid crusting, pain, discomfort, iritis/uveitis

Contraindications

Hypersensitivity to benzalkonium chloride

Counseling Points

- For ophthalmic use only
- To avoid contamination, do not touch tip of container to the eye or to any other surface
- Latanoprost may cause a color change of the iris, increasing the amount of brown pigmentation. This change occurs slowly, may not present for several months to a year, and is likely to be permanent. Latanoprost may cause darkening of the eyelid skin and changes to the eyelashes, including increased thickness, length, and darkening.
- Latanoprost contains benzalkonium chloride, which may be absorbed by contact lenses. Remove contact lenses before instillation of the solution. You may reinsert contact lenses 15 minutes following latanoprost administration.
- If using more than one ophthalmic product, wait at least 5 minutes in between application of each medication
- Storage considerations: Protect this medication from light. Store unopened bottles in the refrigerator. Once opened, you may store the bottle at room temperature for up to 6 weeks.

Key Points

- Prostaglandin analogs are effective agents for the treatment of elevated IOP and glaucoma and in some studies, have demonstrated superior IOP lowering when compared with timolol twice a day. Additionally, with once-daily administration and limited systemic side effects, the prostaglandin analogs are considered first-line therapy in the management of open-angle glaucoma.

- Once-daily dosing should not be exceeded because more frequent administration may decrease the effectiveness of latanoprost
- Although systemic adverse effects are limited, local side effects are notable for changes in iris, eyelid, and eyelash pigmentation

Tafluprost

Mechanism of Action

Tafluprost is a prostaglandin analog; it effectively reduces IOP by increasing aqueous humor outflow from the eye via the uveoscleral pathway

Brand Name

Zioptan (Preservative-Free)

Generic Name

Tafluprost

Rx Only

Dosage Form

Solution

Usage

Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension

Pregnancy Category C

Dosing

Instill 1 drop into the affected eye(s) once daily in the evening

Adverse Reactions: Most Common

Conjunctival hyperemia, ocular stinging/irritation, itching, iris darkening, eyelash darkening, growth of eyelashes, blurry vision

Adverse Reactions: Rare/Severe/Important

Excessive tearing, eyelid crusting, ocular pain, discomfort, iritis/uveitis

Counseling Points

- For ophthalmic use only; wash hands before use
- To avoid contamination, do not touch the tip of the container to the eye or to any other surface
- Administer tafluprost ophthalmic solution immediately after opening single-use container and discard any unused portion immediately after administration. Each single-use container has adequate solution to treat both eyes (if applicable); discard immediately after use.
- If the patient is receiving more than one topical ophthalmic drug, the drugs should be administered at least 5 minutes apart
- Tafluprost may cause a color change of the iris, increasing the amount of brown pigmentation. This change occurs slowly, may not present for several months to a year, and is likely to be permanent. Tafluprost may cause darkening of the eyelid skin and changes to the eyelashes, including increased thickness, length, and darkening.
- Tafluprost does not contain benzalkonium chloride, although it is still recommended to remove contact lenses before instillation of the solution. You may reinsert contact lenses 15 minutes following tafluprost administration.
- Storage considerations: Cartons and unopened foil pouches should be refrigerated and protected from moisture. Once the pouch is opened, single-use containers may be stored in the opened foil pouch at room temperature for up to 28 days.

Key Points

- Prostaglandin analogs are effective agents for the treatment of elevated IOP and glaucoma. Tafluprost has been shown to be noninferior to timolol in reducing IOP in patients with open-angle glaucoma or ocular hypertension. Additionally, with once-daily administration and limited systemic side effects, the prostaglandin analogs are considered first-line therapy in the management of open-angle glaucoma.
- Once-daily dosing should not be exceeded because more frequent administration may decrease the effectiveness of tafluprost
- Preservative-free tafluprost may be useful in patients who have existing corneal damage or hypersensitivity to benzalkonium chloride
- Although systemic adverse effects are limited, local side effects are notable for changes in iris, eyelid, and eyelash pigmentation

Travoprost

Mechanism of Action

Travoprost is a prostaglandin analog; it effectively reduces IOP by increasing aqueous humor outflow from the eye

Brand Name

Travatan Z (benzalkonium-free product)

Generic Name

Travoprost

Rx Only

Dosage Form

Solution

Usage

Treatment of elevated IOP in patients with open-angle glaucoma or ocular hypertension

Pregnancy Category C

Dosing

Instill 1 drop into the affected eye(s) once daily in the evening

Adverse Reactions: Most Common

Darkening of the iris, growth and thickening of the eyelashes, eyelid skin darkening, transient burning and stinging upon instillation, conjunctival hyperemia, itching, blurred vision

Adverse Reactions: Rare/Severe/Important

Excessive tearing, eyelid crusting, pain, discomfort, iritis/uveitis

Counseling Points

- For ophthalmic use only
- To avoid contamination, do not touch tip of container to the eye or to any other surface
- Travoprost may cause a color change of the iris, increasing the amount of brown pigmentation. This change occurs slowly, may not present for several months to a year, and is likely to be permanent. Travoprost may cause darkening of the eyelid skin and changes to the eyelashes, including increased thickness, length, and darkening.
- Remove contact lenses before instillation of the solution. You may reinsert contact lenses 15 minutes following travoprost administration.
- If using more than one ophthalmic drug, separate drugs by at least 5 minutes

Key Points

- Prostaglandin analogs are effective agents for the treatment of elevated IOP and glaucoma and in some studies demonstrated superior IOP lowering when compared with timolol twice a day. Additionally, with once-daily administration and limited systemic side effects, the prostaglandin analogs are considered first-line therapy in the management of open-angle glaucoma.
- Once-daily dosing should not be exceeded because more frequent administration may decrease the effectiveness of travoprost
- Although systemic adverse effects are limited, local side effects are notable for changes in iris, eyelid, and eyelash pigmentation
- Travoprost 0.004% also appears to be superior to timolol 0.5% or latanoprost 0.005% in reducing IOP in African American patients.

◉ Timolol, Timolol-XE

Mechanism of Action

Timolol is a beta-adrenergic blocker. Ophthalmic beta-adrenergic blocking agents decrease IOP by reducing aqueous humor production in the ciliary body of the eye. Nonselective beta blockers (timolol, levobunolol, carteolol, and metipranolol) affect beta-1 and beta-2 receptors, whereas selective beta blockers (betaxolol) affect only beta-1 receptors.

Brand Name

Timoptic, Timoptic-XE, Timoptic GFS, Timoptic Ocudose, Istalol, Betimol

Generic Names

Timolol, timolol-XE

Rx Only

Dosage Forms

Solution, gel-forming solution

Usage

Treatment of elevated IOP in patients with open-angle glaucoma or ocular hypertension

Pregnancy Category C

Dosing

- Solution:
  - Instill 1 drop into the affected eye(s) twice a day; if inadequate response, increase product concentration (0.05%) and instill 1 drop into the affected eye(s) twice daily. Decrease dose to 1 drop once daily if IOP is well controlled
  - Istalol: Instill 1 drop into the affected eye(s) once daily in the morning
- Gel-forming solution (Timolol GFS, Timoptic-XE): Instill 1 drop in the affected eye(s) once daily

Adverse Reactions: Most Common

Temporary burning and stinging following instillation; blurry vision is common for 5 to 10 minutes following administration of the gel-forming solution

Adverse Reactions: Rare/Severe/Important

Local reactions include uveitis, keratitis, superinfection, dry eye, blepharitis, corneal anesthesia, stinging, tearing. Systemic reactions include bradycardia, hypotension, exacerbation of congestive heart failure, bronchospasm, fatigue, dizziness.

Contraindications

Asthma, severe COPD, bradycardia, second- or third-degree AV block, sinus node dysfunction, uncompensated heart failure, cardiogenic shock

Essential Monitoring Parameters

Systemic effects of beta blockade with ophthalmic administration: Blood pressure, heart rate

Counseling Points

- For ophthalmic use only
- To avoid contamination, do not touch tip of container to the eye or to any other surface
- Using proper technique of nasolacrimal occlusion (NLO) is particularly important to optimize efficacy and decrease systemic absorption and toxicities
- Before using, invert gel-forming solution and shake once. Administer other topical ophthalmic medications used concomitantly at least 10 minutes before the gel-forming solution.
- Remove contact lenses before using this medication; wait 15 minutes following administration to reinsert

Key Points

- Ophthalmic beta-adrenergic blockers are generally equally effective in IOP lowering; however, they differ in duration of action, adverse-effect potential, and cost. These agents are considered first-line therapy for the treatment of open-angle glaucoma.
- Because of the risk of systemic adverse events, these drugs are contraindicated in patients with severe pulmonary disease, bradycardia, second- or third-degree heart block, overt heart failure, and cardiogenic shock. If used, clinicians should exercise extreme caution, monitor carefully, and use the lowest effective dose. Patients should practice nasolacrimal occlusion.
- Note: Timoptic-Ocudose does not contain benzalkonium chloride and may be useful in patients receiving multiple ocular products containing preservatives or in those with existing corneal damage

◉ Timolol/Brimonidine

Mechanism of Action

Combigan is composed of timolol, a beta-adrenergic blocker; and brimonidine, an alpha-2 agonist. Ophthalmic beta-adrenergic blocking agents decrease IOP by reducing aqueous humor production in the ciliary body of the eye. Ophthalmic alpha-2 agonists also reduce aqueous humor production; however, they also increase aqueous humor outflow via the uveoscleral pathway of the eye.

Brand Name

Combigan

Generic Names

Timolol/brimonidine

Rx Only

Dosage Forms

Solution

Usage

Treatment of elevated IOP in patients with open-angle glaucoma or ocular hypertension

Pregnancy Category C

Dosing

Instill 1 drop into the affected eye(s) twice a day, approximately 12 hours apart

Adverse Reactions: Most Common

Temporary burning and stinging following instillation, allergic conjunctivitis, itching, conjunctival hyperemia, conjunctival folliculosis, excessive tearing

Adverse Reactions: Rare/Severe/Important

Local adverse reactions include blepharitis, blurred vision, corneal erosion, eye pain, eyelid edema, eyelid erythema, superficial punctuate keratitis. Systemic adverse reactions include hypertension, bradycardia, exacerbation of congestive heart failure, bronchospasm, fatigue, dizziness.

Contraindications

Asthma, severe COPD, bradycardia, second- or third-degree AV block, sinus node dysfunction, uncompensated heart failure, cardiogenic shock

Essential Monitoring Parameters

Systemic effects of beta blockade with ophthalmic administration: blood pressure, heart rate

Counseling Points

- For ophthalmic use only
- To avoid contamination, do not touch tip of container to the eye or to any other surface
- Using proper technique of nasolacrimal occlusion (NLO) is particularly important to optimize efficacy and decrease systemic absorption and toxicities
- Separate administration of other ophthalmic products by at least 5 minutes
- Remove contact lenses before using this medication; wait 15 minutes following administration to reinsert

Key Points

- Combigan is a combination product composed of a nonselective beta-adrenergic blocker (timolol) and an alpha-adrenergic agonist (brimonidine)
- Ophthalmic alpha-agonists have been associated with a localized allergic-type reaction characterized by eyelid edema, erythema, itching, discomfort, and foreign object sensation. Among the alpha-agonists, brimonidine has the lowest incidence of this side effect, affecting approximately 5% to 9% of patients in clinical trials.
- Because of the risk of systemic adverse events with ophthalmic beta blockers, these drugs are contraindicated in patients with severe pulmonary disease, bradycardia, second- or third-degree heart block, overt heart failure, and cardiogenic shock. If used, clinicians should exercise extreme caution, monitor carefully, and use the lowest effective dose. Patients should practice nasolacrimal occlusion.

ANTIHISTAMINES

Introduction

Allergic conjunctivitis is an allergic-type reaction occurring in the conjunctiva of the eye in response to a specific allergen. It is commonly seasonal and is usually associated with exposure to pollen, ragweed, dust, or mold spores. Pharmacotherapy options used to treat acute episodes of allergic conjunctivitis include artificial tears and combination topical antihistamines/topical vasoconstrictor products. For frequent episodes or seasonal and perennial allergies, the agents of choice are topical antihistamines and mast cell stabilizers. It takes 5 to 14 days to see optimal effects with mast cell stabilizers, thus they are best initiated 2 to 4 weeks before allergy exposure rather than as treatment for acute symptoms. The agents discussed in this section, ketotifen and olopatadine, possess both antihistamine and mast cell–stabilizing properties. They are considered drugs of choice because they effectively work on both the chronic and acute symptoms of allergic conjunctivitis.

Mechanism of Action for the Drug Class

These agents block the effects of histamine by selectively blocking H1 receptors. They also exhibit mast cell–stabilizing properties, preventing mast cell degranulation, which is the first step in the allergy cascade.

Usage for the Drug Class

Allergic conjunctivitis

Pregnancy Category C for the Drug Class

Adverse Reactions for the Drug Class: Most Common

Localized discomfort and irritation, transient burning, pain or stinging, dry eye, itching, redness, tearing, foreign body sensation. Systemic adverse reactions include flu-like symptoms, headache, pharyngitis, rhinitis

Adverse Reactions for the Drug Class: Rare/Severe/Important

Secondary infection, decreased vision, hypersensitivity, keratitis, photophobia, rash

Counseling Points for the Drug Class

- For ophthalmic use only
- To avoid contamination, do not touch tip of container to eye or any other surface
- Remove contact lenses before using this medication; wait 15 minutes following administration to reinsert. Should not be used to treat contact lens–related irritation.
- If using a topical antihistamine as a self-care product, seek medical advice if symptoms do not improve within 48 to 72 hours

Key Points for the Drug Class

- Occasional, acute onset allergic conjunctivitis is best treated with a combination topical antihistamine/vasoconstrictor product, artificial tears, and cold compress
- Frequent episodes or seasonal/perennial allergic conjunctivitis are best treated with a dual-action antihistamine/mast cell–stabilizing agents, which are effective at acute relief of symptoms and chronic management of the condition

Members of the Drug Class

In this section: Olopatadine, ketotifen.
Others: Azelastine, epinastine, bepotastine, alcaftadine, emedastine, pheniramine
Mast cell stabilizers: Cromolyn sodium, nedocromil sodium, lodoxamide, pemirolast

◉ Ketotifen

Brand Names

Alaway, Claritin Eye, Zaditor, Zyrtec Itchy Eye, Eye Itch Relief, TheraTears Allergy

Generic Name

Ketotifen

OTC

Dosage Form

Solution

Dosing

Instill 1 drop into the affected eye(s) twice a day at an interval of every 8 to 12 hours; do not exceed 2 applications/day. This product is safe for use in children ≥ 3 years old and adolescents.

◉ Olopatadine

Brand Names

Pataday, Patanol, Pazeo

Generic Name

Olopatadine

Rx Only

Dosage Form

Solution

Dosing

- Pataday, Pazeo: Instill 1 drop into the affected eye(s) once a day; safe in children ≥ 2 years and adolescents
- Patanol: Instill 1 drop into the affected eye(s) twice a day (6 to 8 hours between doses); safe in children ≥ 3 years old and adolescents

CORTICOSTEROIDS

Introduction

Ophthalmic steroids are applied topically for a variety of inflammatory conditions, including allergic conjunctivitis, uveitis, iritis, and superficial punctate keratitis. In addition, these agents are often used in the setting of chemical, thermal, or foreign body injury to the eye and in the immediate postocular surgical setting to decrease inflammation and scar tissue formation. Steroids may delay wound healing, so they are generally not recommended for minor abrasions or injury. In general, steroids do not have a role in the treatment of simple conjunctivitis and should not be used in most cases of viral conjunctivitis; their use may prolong and exacerbate the severity of viral ocular infections. Prolonged use of ophthalmic steroids may lead to elevated intraocular pressure (IOP) and damage to the optic nerve. Caution is advised when using these agents in patients with primary open-angle glaucoma or elevated IOP.

Mechanism of Action for the Drug Class

The exact mechanism of corticosteroids' action is unknown. Their anti-inflammatory action is likely related to their ability to inhibit edema, fibrin deposition, capillary dilation, and leukocyte migration. They are also known to decrease the activity of inflammatory mediators, such as prostaglandins and leukotrienes.

Members of the Drug Class

In this section: Loteprednol
Others: Dexamethasone, difluprednate, fluocinolone (ocular implant), fluorometholone, prednisolone, rimexolone, triamcinolone (ocular injection)

◉ Loteprednol

Brand Names

Lotemax, Alrex

Generic Name

Loteprednol

Rx Only

Dosage Forms

Suspension, ointment, gel

Usage

Various ocular inflammatory conditions, allergic conjunctivitis, postoperative pain, and inflammation following ocular surgery

Pregnancy Category C

Dosing

- Allergic conjunctivitis:
  - Loteprednol 0.2% suspension (Alrex): Instill 1 drop into the affected eye(s) 4 times a day
- Inflammatory conditions:
  - Loteprednol 0.5% suspension (Lotemax): Instill 1 to 2 drops into the affected eye(s) 4 times a day; during initial week of therapy, dose may be increased to a maximum of 1 drop every hour, if necessary
- Postoperative inflammation:
  - Loteprednol 0.5% suspension or gel (Lotemax): Instill 1 to 2 drops into the affected eye(s) 4 times a day beginning 24 hours after surgery and continuing through the first 2 weeks of the postoperative period
  - Loteprednol 0.5% ointment (Lotemax): Apply 0.5-inch ribbon into the conjunctival sac of the affected eye(s) 4 times a day beginning 24 hours after surgery and continuing through the first 2 weeks of the postoperative period

Adverse Reactions: Most Common

Transient burning, stinging, irritation upon instillation; foreign body sensation; chemosis; itching; dry eye; excessive tearing; blurry vision; photophobia. Systemic effects include headache, rhinitis, and pharyngitis.

Adverse Reactions: Rare/Severe/Important

Visual changes/decreased vision, elevated IOP, optic nerve damage, glaucoma, secondary infections (bacterial, viral, fungal), cataract formation

Contraindications

Viral, mycobacterial, and fungal infections of the cornea and conjunctiva

Essential Monitoring Parameter

IOP if use is > 10 days

Counseling Points

- For ophthalmic use only
- To avoid contamination, do not touch tip of container to the eye or to any other surface
- Loteprednol contains benzalkonium chloride, which may be absorbed by contact lenses Remove contact lens before instillation of the solution. You may reinsert contact lenses 15 minutes following loteprednol administration.

Key Points

- Common adverse effects, including stinging, irritation, and burning, are usually transient and not harmful
- Generally, application of ophthalmic corticosteroids does not provide enough systemic absorption to cause severe systemic side effects and is not associated with HPA-axis suppression
- Duration of use >10 days should only occur under the direct supervision of a physician and with careful monitoring of IOP. Long-term use of these agents has

been associated with increased IOP in some patients. Ophthalmic dexamethasone is the most frequently reported corticosteroid eye drop to cause elevated IOP.
- Loteprednol was developed as a "site-specific steroid" and has less of an effect on IOP due to its high lipophilicity and rapid metabolism. It is frequently prescribed to prevent and treat seasonal allergies; however, use for > 14 days should only occur under the supervision of a medical professional.
- Prolonged use of ocular corticosteroids may increase the incidence of secondary infection, mask acute infection, or prolong or exacerbate viral infections

COMBINATION ANTIBIOTIC/CORTICOSTEROID AGENTS

Introduction

Combination antibiotic/corticosteroid ophthalmic products are used in a variety of conditions in which a corticosteroid is indicated and in which superficial bacterial infection or risk of infection exists. The steroid component suppresses the inflammatory response; however, it is also likely to delay or slow wound healing. Because corticosteroids may inhibit the body's defense mechanisms against infection, a concomitant antimicrobial agent may be used when this inhibition is considered to be clinically significant. Topical ophthalmic steroids are not recommended for long-term use; prolonged use may lead to elevated IOP and the development of glaucoma.

Members of the Drug Class

In this section: Tobramycin/dexamethasone
Others: Multiple combination products are available containing the following antibacterial agents: Neomycin, neomycin/polymyxin B, gentamicin, tobramycin, chloramphenicol, bacitracin, sulfacetamide; multiple combination products are available containing the following steroid components: Hydrocortisone, prednisolone, dexamethasone, loteprednol

◉ Tobramycin/Dexamethasone

Mechanism of Action

Dexamethasone is a potent corticosteroid that inhibits the inflammatory response by inhibiting interleukin-1 and various other cytokines that mediate inflammatory responses. It also decreases inflammation by suppressing the migration of polymorphonuclear leukocytes and decreasing capillary permeability. Tobramycin is an aminoglycoside antibiotic that provides activity against susceptible organisms by irreversibly binding to the 30S ribosomal subunit, disrupting bacterial protein synthesis, and causing cell death.

Brand Name

TobraDex, TobraDex ST

Generic Name

Tobramycin/dexamethasone

Rx Only

Dosage Forms

Suspension, ointment

Usage

Steroid-responsive inflammatory ocular conditions with infection or risk of infection; chronic anterior uveitis; corneal injury from chemical, radiation or thermal burns; penetration of foreign bodies

Pregnancy Category C

Dosing

- Suspension:
  - Instill 1 or 2 drops into the affected eye(s) every 4 to 6 hours
  - Severe infections: Instill 1 or 2 drops every 2 hours for the first 24 to 48 hours, and then decrease administration to every 4 to 6 hours
- Ointment:
  - Apply 0.5-inch ribbon to the conjunctival sac of the affected eye(s) every 6 to 8 hours
  - Severe infections: Apply 0.5-inch ribbon to the conjunctival sac every 3 to 4 hours for the first 24 to 48 hours, and then decrease administration to every 6 to 8 hours

Adverse Reactions: Most Common

Superinfection, itching, and swelling

Adverse Reactions: Rare/Severe/Important

Visual changes/decreased vision; hypersensitivity reaction manifested as itching, redness, and edema of the eyelid; optic nerve damage; glaucoma; secondary infections (bacterial, viral, fungal)

Contraindications

Viral, mycobacterial, and fungal infections of the cornea and conjunctiva

Essential Monitoring Parameter

IOP if use is > 10 days

Counseling Points

- For ophthalmic use only
- Store suspensions upright and shake well before using
- To avoid contamination, do not touch tip of container to the eye or to any other surface
- Do not wear contact lenses during the use of this product; the suspension contains benzalkonium chloride, which may be absorbed by contact lenses

Key Points

- Prolonged use of ophthalmic corticosteroids is associated with risk of elevated IOP, damage of the optic nerve, development of glaucoma, secondary infections, and thinning/perforation of the cornea or sclera in susceptible patients
- Prolonged use of ophthalmic corticosteroids in combination with antibiotics may increase the incidence of secondary infection, mask acute infection, or prolong or exacerbate viral infections

REVIEW QUESTIONS

1. Which of the following statements is correct regarding the benefits of nasolacrimal occlusion?
   a. Improves the bioavailability of an ophthalmic medication
   b. Increases the risk of systemic side effects
   c. Decreases the risk of systemic side effects
   d. A and C

2. Which of the following statements regarding application of an antibiotic ophthalmic ointment is *false?*
   a. Proper aseptic technique begins with washing your hands
   b. Proper administration technique helps prevent superinfection
   c. Apply a 0.25–0.5 inch ribbon on the upper eyelid for best absorption
   d. Blurry vision is common for up to 20 minutes following administration

3. GW is a 62-year-old male with a past medical history of severe COPD, HTN, and a new diagnosis of open-angle glaucoma. Which of the following medications would be contraindicated for use in GW to treat his glaucoma?
   a. Travatan Z
   b. Betimol
   c. Xalatan
   d. Zioptan

4. Which of the following "generic name—brand name" pairs are *not* correctly matched?
   a. Travoprost–Travatan Z
   b. Olopatadine–Zaditor
   c. Gatifloxacin–Zymar
   d. Loteprednol–Alrex

5. Which of the following is a contraindication to the use of TobraDex?
   a. Allergic conjunctivitis
   b. Corneal injury from a chemical burn
   c. Viral and fungal infections of the cornea and conjunctiva
   d. Chronic uveitis

6. Which of the following agents is available as a preservative-free ophthalmic solution?
   a. Ketotifen
   b. Tafluprost
   c. Ciprofloxacin
   d. Timolol/brimonidine

7. Tobramycin belongs to which of the following classes of antibacterial agents?
   a. Fluoroquinolone
   b. Beta-lactam
   c. Macrolide
   d. Aminoglycoside

8. Which of the following counseling points are correct for Travoprost?
   a. Travoprost is superior to timolol in lowering IOP in African-American patients
   b. A well-known adverse effect is eyelash thickening
   c. Twice daily dosing may increase the effectiveness of travoprost
   d. Travoprost does not contain benzalkonium chloride as a preservative

9. When using ophthalmic products, patients should be counseled about all of the following, *except:*
   a. For most products, contact lenses should be removed prior to administration
   b. Contamination can occur if the product tip touches the surface of the eye
   c. Store preservative-free products at room temperature to use for multiple doses
   d. Nasolacrimal occlusion is most effective for ophthalmic solutions and suspensions

10. Which of the following drug:mechanism of action pairs is *incorrect?*
   a. Loteprednol increases the activity of inflammatory mediators
   b. Moxifloxacin inhibits the activity of DNA gyrase
   c. Travoprost reduces IOP by increasing aqueous humor outflow from the eye
   d. Neosporin alters the permeability of the cell membrane, leading to cell death

11. Which of the following is *not* a common adverse reaction to erythromycin ointment?
   a. Red eye
   b. Eye irritation
   c. Eyelid darkening
   d. Blurred vision

12. Which of the following agents should be used to treat bacterial conjunctivitis?
   a. Istalol
   b. Zioptan
   c. Zymaxid
   d. TobraDex

13. Which of the following statements regarding ophthalmic beta blockers is *false?*
   a. Timolol-XE should be dosed once daily
   b. Betaxolol is a selective beta-1 receptor blocker
   c. Ophthalmic beta blockers are considered first-line agents in the treatment of glaucoma
   d. Routine monitoring of systemic side effects of beta blockade is not necessary

14. Which of the following agents may be used for long-term treatment of ocular hypertension?
   a. Patanol
   b. Combigan
   c. Neosporin
   d. Alrex

15. Which of the following ophthalmic agents is most likely to have systemic adverse effects potentially limiting its use?
   a. Xalatan
   b. Timoptic GFS
   c. TobraDex
   d. Ciloxan

16. Which of the following statements is true regarding ophthalmic erythromycin ointment?
   a. Contact lenses may be worn while using erythromycin ointment
   b. Erythromycin ointment is used routinely to prevent ophthalmia neonatorum
   c. Blurry vision may last for hours after administration of erythromycin ointment
   d. Erythromycin ointment is effective for the treatment of neonatal *Chlamydia oc*ular infections

17. The active ingredients in Neosporin Ophthalmic Solution include:
   a. Neomycin, bacitracin, polymyxin B
   b. Neomycin, polymyxin B, hydrocortisone
   c. Neomycin, polymyxin B, gramicidin
   d. Neomycin, polymyxin B, dexamethasone

18. Which of the following statements is false regarding Lotemax?
   a. Damage to the optic nerve can occur with prolonged use of Lotemax
   b. Lotemax is preferred in the treatment of viral conjunctivitis
   c. Systemic side effects include headache and rhinitis
   d. For postoperative inflammation, continue treatment for 2 weeks after surgery

19. Which of the following prescriptions for Combigan is correct?
   a. Instill 1 drop into the affected eye(s) once daily in the evening
   b. Instill 1 drop into the affected eye(s) twice a day, approximately 12 hours apart
   c. Instill 2 drops into the affected eye(s) twice a day, approximately 12 hours apart
   d. Instill 1 drop into the affected eye(s) 4 times a day

20. Which of the following statements is *true* regarding brimonidine?

- **a.** Brimonidine has been associated with a greater degree of IOP lowering than timolol
- **b.** Brimonidine has been associated with systemic side effects such as hypotension and bradycardia
- **c.** Brimonidine has been associated with an allergic-type reaction in a small percentage of patients in clinical trials
- **d.** Brimonidine is contraindicated in severe asthma or COPD

21. A patient brings in a prescription to treat bacterial conjunctivitis. Her profile indicates that she has an allergy to fluoroquinolones. Which of the following antibiotics could you recommend?

- **a.** Moxeza
- **b.** Neosporin
- **c.** Zymar
- **d.** Alrex

22. Which of the following is the generic name for Claritin Eye?

- **a.** Loratadine
- **b.** Neomycin
- **c.** Ketotifen
- **d.** Tafluprost

23. Which of the following statements is true regarding allergic conjunctivitis?

- **a.** The recommended duration of treatment with topical antihistamines is 5 to 7 days
- **b.** Mast cell stabilizers should be initiated 2 to 4 weeks before allergy season
- **c.** Pazeo is available without a prescription
- **d.** Zaditor is only effective for the acute symptoms of allergic conjunctivitis

24. Which of the following agents is *not* indicated for the treatment of glaucoma?

- **a.** Tafluprost
- **b.** Brimonidine
- **c.** Olopatadine
- **d.** Timolol

25. Ophthalmic beta blockers have been associated with the following systemic adverse effects *except:*

- **a.** Fatigue
- **b.** Worsening heart failure
- **c.** Hypotension
- **d.** Migraine headaches

26. In which of the following situations would loteprednol be contraindicated for use?

- **a.** A 27-year-old man with a chemical burn injury to the eye
- **b.** A 56-year-old woman with a mycobacterial infection of the conjunctiva
- **c.** A 33-year-old man with inflammation of the iris, or iritis
- **d.** A 78-year-old woman who is recovering from ocular surgery and has developed inflammation

27. Which of the following statements regarding Zioptan is true?

- **a.** It works by decreasing aqueous humor outflow via the uveoscleral pathway
- **b.** Cartons and unopened pouches should be stored at room temperature
- **c.** Zioptan may be useful in patients who have existing corneal damage
- **d.** Zioptan containers can be used for multiple doses if stored in the refrigerator

28. Prostaglandin analogs are considered first line in the treatment of glaucoma. Although this class is relatively well-tolerated, all of the following are potential side effects, EXCEPT:

- **a.** Increased iris pigmentation
- **b.** Transient burning upon instillation
- **c.** Decreased heart rate
- **d.** Increased eyelash length

29. Which product contains an antihistamine and a mast cell stabilizer?

- **a.** Pataday
- **b.** Combigan
- **c.** TobraDex
- **d.** Neosporin

30. Which of the following is NOT recommended for the treatment of allergic conjunctivitis?

- **a.** Ketotifen
- **b.** Tobramycin/dexamethasone
- **c.** Olopatadine
- **d.** Loteprednol

CHAPTER 13

Pulmonary and Allergy Agents

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ANTICHOLINERGICS, INHALED

Introduction

Anticholinergic inhalers and nasal preparations are primarily used for chronic obstructive pulmonary disease (COPD), asthma, allergic and nonallergic rhinitis, and nasal cold symptoms. Ipratropium is a short-acting agent used during acute asthma and COPD exacerbations but in combination with short-acting beta-adrenergic agonists. Ipratropium may also be used as a short-acting rescue inhaler in patients with COPD. Tiotropium Respimat® is the only long-acting inhaled anticholinergic used in the chronic treatment of asthma not responding to therapy with moderate-high dose inhaled corticosteroids and long-acting beta-2 agonists. Other long-acting anticholinergics are used in the chronic treatment of COPD. The most common adverse reaction associated with the inhalation preparations is dry mouth, upper respiratory tract infections, and nasopharyngitis.

Mechanism of Action for the Drug Class

The drug class appears to produce bronchodilation by blocking acetylcholine at muscarinic receptors, therefore, blocking the direct constrictor effects of acetylcholine on bronchial smooth muscle. Ipratropium blocks all muscarinic receptors. Local application to nasal mucosa inhibits mucous gland secretions. Glycopyrrolate competitively and reversibly inhibits acetylcholine at the muscarinic receptor subtypes, 1 and 3, which cause bronchodilation. Tiotropium, aclidinium, and umeclidinium are long-acting agents, selective to the M3 receptors.

Members of the Drug Class

In this section: Ipratropium, glycopyrrolate, aclidinium, tiotropium and umeclidinium
Others: None

Adverse Reactions: Most Common

Cough, dry mouth, dyspepsia, dizziness, blurred vision, headache, sore throat, nasal irritation (nasal spray), epistaxis (nasal spray), taste perversion

Adverse Reactions: Rare/Severe/Important

Paradoxical bronchospasms; worsening of narrow-angle glaucoma/mydriasis; increased intraocular pressure (especially if sprayed into eyes); worsening of urinary retention

Major Drug Interactions

Drugs Affecting Inhaled Anticholinergics

Other anticholinergics or drugs that have anticholinergic properties: May enhance effects

Contraindications

None

◉ Ipratropium

Brand Name

Atrovent HFA

Generic Name

Ipratropium

Rx

Dosage Forms

Aerosol for oral inhalation, solution for nebulizer, nasal spray

Usage

COPD, adjunct in acute asthma exacerbations, allergic and nonallergic rhinitis (nasal spray 0.03%), common cold (nasal spray 0.06%)

Pregnancy Category B

Dosing

- COPD:
  - 2 puffs inhaled by mouth 4 times a day (doses 6 to 8 hours apart)
  - Maximum dose: 12 puffs per day

- Solution for nebulizers:
  - 500 µg inhaled by mouth three to four times a day (doses 6 to 8 hours apart)
  - Maximum dose: 2 mg every 24 hours
- Acute asthma exacerbation (in combination with short-acting beta-adrenergic agonists):
  - Inhaler: 8 inhalations every 20 minutes as needed for less than or equal to 3 hours
  - <12 years: 4 inhalations every 20 minutes as needed for less than or equal to 3 hours
  - Solution for nebulizer: 500 µg every 20 minutes for 3 doses, then as needed
  - <12 years: 250 µg every 20 minutes for 3 doses, then as needed
- Allergic/nonallergic rhinitis, nasal spray 0.03%:
  - 2 puffs in each nostril 2 to 3 times a day
  - Maximum dose: 12 puffs every 24 hours
- Common cold, nasal spray 0.06%:
  - 2 puffs in each nostril 3 to 4 times a day
  - Maximum dose: 16 puffs every 24 hours

Counseling Points

- Use proper administration technique
- The Atrovent HFA inhalation aerosol does not have to be shaken before use
- Avoid spraying into eyes
- Directions for proper use of aerosol for oral inhalation:
  1. The inhaler must be "primed" 2 times before taking the first dose from a new inhaler or when the inhaler has not been used for more than 3 days
  2. Insert the metal canister into the top of the mouthpiece and remove the protective dust cap from the mouthpiece
  3. Exhale deeply through your mouth
  4. Put the mouthpiece in your mouth and close your lips. Keep your eyes closed so the medicine will not spray into your eyes.
  5. Inhale slowly through your mouth and, at the same time, press firmly once on the canister, continuing to breathe deeply
  6. Hold your breath for 10 seconds or for as long as you feel comfortable
  7. Exhale slowly
  8. Wait at least 15 seconds before repeating steps 1 through 7 for the next inhalation
  9. Replace the dust cap after use
  10. Keep the mouthpiece clean. Wash it at least once a week. Shake it to remove excess water and let it air dry.
- Mouthpiece cleaning instructions:
  1. Remove and set aside the canister and dust cap from the mouthpiece
  2. Wash the mouthpiece through the top and bottom with warm running water for at least 30 seconds. Do not use anything other than water to wash the mouthpiece.
  3. Dry the mouthpiece by shaking off the excess water and allow it to air dry
  4. When the mouthpiece is dry, replace the canister. Make sure the canister is fully and firmly inserted into the mouthpiece.
- If using more than the prescribed amount, contact your healthcare provider
- Use with a proper spacing device

Key Points

- Most commonly used for the treatment of acute bronchospasms in COPD and as an adjunct in asthmatic patients
- Most common adverse reaction is dry mouth and nasal irritation with nasal spray
- Inform patients with glaucoma or urinary retention to report worsening symptoms after use of this agent

Aclidinium

Brand Name

Tudorza Pressair

Generic Name

Aclidinium

Rx

Dosage Forms

400 µg aerosol powder per inhalation

Usage

Maintenance treatment of COPD

Pregnancy Category C

Dosing

One inhalation (400 µg) inhaled orally twice daily

Contraindications

Tudorza Pressair contains lactose. Avoid use in patients with severe hypersensitivity to milk proteins.

Counseling Points

- Should not be used to treat acute bronchospasms
- The dose indicator tells you how many doses are left
- Discard inhaler 45 days after removing the inhaler from the sealed pouch or after the labeled number of inhalations have reached zero (whichever occurs first)
- Directions for proper administration technique:
  1. Prior to each use, remove protective cap from the inhaler and prepare the inhaler by pressing and releasing the green button (while keeping the green button straight up and avoiding tilting the inhaler)

2. The inhaler is ready for use when the colored control window changes from red to green
3. Prior to inhaling the dose, exhale fully (do not exhale into the inhaler), then close lips tightly around the inhaler mouthpiece and inhale (rapidly, steadily, and deeply); do not hold the green button down while inhaling
4. Keep breathing in until a "click" is heard to ensure that the full dose has been administered
5. Hold breath as long as possible, then breathe out slowly through nose
6. Ensure that the dose was delivered correctly by observing the control window, which should have changed from green to red. If the control window is still green, repeat inhalation steps. When control window has been verified as red, replace the protective cap on the inhaler for the next use.

Key Points

- Use for chronic treatment of COPD; should not be used to treat acute bronchospasms
- Inform patients with glaucoma or urinary retention to report worsening symptoms after use of this agent

◉ Glycopyrrolate

Brand Name

Seebri Neohaler

Generic Name

Glycopyrrolate

Rx

Dosage Forms

Capsule for oral inhalation. Each capsule contains 15.6μg glycopyrrolate, delivered via a special dry powder inhaler device (Neohaler) for oral inhalation only.

Usage

Maintenance treatment of COPD

Pregnancy Category

- Adverse events have been observed in some animal reproduction studies
- Small amounts of glycopyrrolate cross the human placenta following IM injection

Dosing

Contents of one capsule (15.6 μg) inhaled orally twice daily using the Neohaler

Contraindications

Seebri Neohaler contains lactose. Avoid use in patients with severe hypersensitivity to milk proteins.

Counseling Points

- Should not be used to treat acute bronchospasms
- Capsule is for inhalation only via the Neohaler device; do not swallow capsules
- If a dose is missed, administer the next capsule at the usual time; do not use two capsules at one time and do not use >2 capsules/day (maximum: 31.2 μg of glycopyrrolate/day)
- Use proper administration technique via the Neohaler device:
  1. Pull off cap to expose mouthpiece
  2. Hold the base of the inhaler firmly and tilt the mouthpiece to open the inhaler
  3. Remove capsule from blister pack. Do not open capsule.
  4. Insert capsule into capsule chamber. It does not matter which end of the capsule you put in the chamber.
  5. Close the mouthpiece until you hear a "click"
  6. Hold the inhaler upright and pierce the capsule by firmly pressing together both side buttons at the same time (do this only once); a click sound should be heard when capsule is being pierced
  7. Release the side buttons fully
  8. Breathe out completely. Do not exhale into the mouthpiece.
  9. Breathe in rapidly, steadily, and deeply so you hear or feel the capsule vibrate
  10. Hold your breath for at least 5 to 10 seconds or for as long as you comfortably can while taking the inhaler out of your mouth
  11. To get the full dose of the medication, you must breathe out completely and repeat steps 8 through 10

Key Points

- Use for chronic treatment of COPD; should not be used to treat acute bronchospasms
- Capsule should be inhaled via Neohaler only and should not be swallowed
- Inform patients with glaucoma or urinary retention to report worsening symptoms after use of this agent

◉ Tiotropium

Brand Names

Spiriva HandiHaler, Spiriva Respimat

Generic Name

Tiotropium

Rx

Dosage Forms

Capsule containing inhalation delivered via a special dry powder inhaler device (HandiHaler) for oral inhalation only, Respimat device

Usage

Maintenance treatment of COPD, maintenance treatment of asthma

Pregnancy Category C

Dosing

- Respimat:
  - Adults and children ≥ 6 years old, asthma: 2.5 µg (2 inhalations if 1.25 µg) once daily
  - Adults, COPD: 5 µg (2 inhalations of 2.5 µg) once daily
- HandiHaler:
  - Adults, COPD: Contents of one capsule (18 µg) inhaled orally once daily

Contraindications

None

Counseling Points

- Capsule is for inhalation only via the HandiHaler device; do not swallow
- Should not be used to treat acute bronchospasms
- Directions for proper use of the HandiHaler device:
  1. Open the HandiHaler device. Pull the cap upward to expose the mouthpiece.
  2. Open the mouthpiece by pulling the mouthpiece ridge upward away from the base
  3. Remove the capsule from the blister pack. Do not open the capsule.
  4. Insert the capsule into the center chamber of the HandiHaler device. It does not matter which end of the capsule you put in the chamber.
  5. Close the mouthpiece until you hear a click but leave the cap open
  6. Hold the HandiHaler device with the mouthpiece upright
  7. Press the green button until it is flat against the base and release
  8. Breathe out completely. Do not exhale into the mouthpiece.
  9. Hold the HandiHaler device by the gray base and raise the device to your mouth. Close your lips tightly around the mouthpiece.
  10. Breathe in slowly and deeply so you hear or feel the capsule vibrate
  11. Hold your breath as long as it is comfortable and, at the same time, take the inhaler out of your mouth
  12. To get the full dose of the medication, you must breathe out completely and repeat steps 9 through 11. Do not press the green button again.
  13. After you finish taking your daily dose, open the mouthpiece again. Tip out the used capsule and throw it away.
  14. Close the mouthpiece cap for storage of your HandiHaler

Key Points

- Used for chronic treatment of COPD and asthma
- Tiotropium should not be used to treat acute bronchospasms
- Capsule should be inhaled via HandiHaler only and should not be swallowed
- Do not spray directly into eyes
- Inform patients with glaucoma or urinary retention to report worsening symptoms after use of this agent

◉ Umeclidinium

Brand Name

Incruse Ellipta

Generic Name

Umeclidinium

Rx

Dosage Forms

62.5 µg aerosol powder per inhalation

Usage

Maintenance treatment of COPD

Pregnancy Category C

Dosing

Contents of one inhalation (62.5 µg) inhaled orally once daily (this is also the maximum dose)

Contraindications

Incruse® Ellipta® contains lactose. Avoid use in patients with severe hypersensitivity to milk proteins.

Counseling Points

- The dose indicator tells you how many doses are left
- If you open and close the cover without inhaling the medicine, you will lose the dose
- Discard inhaler 6 weeks after opening the foil tray or after the labeled number of inhalations have reached zero (whichever comes first)
- Use proper administration technique:
  1. When you are ready to inhale a dose, open the cover of the inhaler and slide the cover down to expose the mouthpiece. You should hear a "click." The counter will count down by one number. You do not need to shake this kind of inhaler.
  2. Exhale fully; do not breathe out into the mouthpiece.
  3. Put the mouthpiece between your lips and close your lips firmly around it.
  4. Take one long, steady, deep breath in through your mouth
  5. Do not block the air vent with your fingers

6. Remove the inhaler from your mouth
7. Hold your breath for 3 to 4 seconds (or as long as is comfortable)
8. Breathe out slowly and gently
9. Close the lid of the inhaler.

Key Points

- Use for chronic treatment of COPD and should not be used to treat acute bronchospasms
- Inform patients with glaucoma or urinary retention to report worsening symptoms after use of this agent

ANTIHISTAMINES, FIRST GENERATION, SEDATING

Introduction

The first-generation antihistamines are used primarily for hypersensitivity/allergic reactions, sleep disorders, and as antiemetics or for preventing motion sickness. They are not typically used chronically for allergic rhinitis due to the potential for sedation, but they are still used in some cases because many of these agents are available without a prescription. These agents are generally used on an as-needed basis, depending on the indication. Chronic use of these agents should be avoided in the elderly due to their sedative and anticholinergic effects. Sedation is the most common adverse reaction associated with these agents, and concomitant drugs that cause sedation should be avoided.

Mechanism of Action for the Drug Class

These agents reversibly, competitively antagonize H1 receptors peripherally and centrally, blocking the increased capillary permeability (edema/wheel formation) and itching caused by histamine release. Diphenhydramine and promethazine have the most significant anti-muscarinic properties, which lead to their anti-emetic effects and lessen rhinorrhea in the common cold.

Adverse Reactions for the Drug Class: Most Common

Drowsiness, somnolence, fatigue, dizziness, headache, nausea, nervousness, tremor, dry mouth

Major Drug Interactions for the Drug Class

Drugs Affecting Antihistamines

- Alcohol and CNS depressants: Potentiate drowsiness
- Other anticholinergic drugs: Potentiate side effects

Members of the Drug Class

In this section: Diphenhydramine, hydroxyzine, promethazine
Others: Brompheniramine, chlorpheniramine, clemastine doxylamine, triprolidine

◉ Diphenhydramine

Brand Name

Benadryl

Generic Name

Diphenhydramine

Rx (Injectable) and OTC

Dosage Forms

Capsule, tablet, chewable tablet, liquid, injection, topical cream

Usage

Allergic dermatitis, hypersensitivity reactions, allergic reactions, sleep disorders, allergic rhinitis, antitussive, motion sickness, treatment of drug-induced extrapyramidal reactions

Pregnancy Category B

Dosing

- Children:
  - <2 years: Use not recommended due to dosing errors and accidental ingestion
  - 2 to 6 years:
    - 6.25 mg PO every 4 to 6 hours
    - Maximum dose: 37.5 mg every 24 hours
  - 6 to 12 years:
    - 12.5–25 mg PO every 4 to 6 hours
    - Maximum dose: 150 mg every 24 hours
  - >12 years: See adult dosing
- Adults:
  - 25–50 mg PO every 4 to 8 hours
  - Maximum dose: 300 mg every 24 hours

Adverse Reactions: Rare/Severe/Important

Excitation in young children, high risk of sedation and dizziness in elderly

Contraindications

Neonates and premature infants

Counseling Points

- Young children may experience a paradoxical excitation effect

- Tolerance to CNS effects may develop quickly; sedation will no longer be troublesome after a few days
- For motion sickness, take the dose 30 minutes to 1 hour before traveling

Key Points

- Diphenhydramine is commonly used for allergies, motion sickness, and sleep disorders
- Sedation is the most common adverse reaction
- Not recommended for use in children < 2 years of age
- May be inappropriate to use in the elderly due to sedative and anticholinergic effects

Hydroxyzine

Brand Names

Atarax, Vistaril

Generic Name

Hydroxyzine

Rx

Dosage Forms

Tablet, capsule, syrup, IM injection

Usage

Pruritus, sedation, anxiety, motion sickness, nausea and vomiting

Pregnancy Category C

Dosing

- Pruritus:
  - Children:
    - 2 to 6 years:
      - 12.5 mg PO every 6 hours, as needed
      - Maximum dose: 50 mg every 24 hours
    - 6 to 12 years:
      - 12.5–25 mg PO every 6 hours, as needed
      - Maximum dose: 100 mg every 24 hours
    - > 12 years: See adult dosing
  - Adults:
    - 25 mg PO every 6 to 8 hours
    - Maximum dose: 400 mg every 24 hours
- Sedation:
  - Children:
    - 0.6 mg/kg PO as a single dose
    - Maximum dose: Not to exceed 50 mg as a single dose
  - Adults:
    - Oral: 50–100 mg as a single dose
    - IM injection: 50 mg as a single dose
- Hepatic dosage adjustment: Change dosing interval to every 24 hours in patients with primary biliary cirrhosis

Adverse Reactions: Common

Sedation

Adverse Reactions: Rare/Severe/Important

QT prolongation, acute generalized exanthematous pustulosis

Contraindications

Early pregnancy; intravenous, subcutaneous, or intra-arterial administration

Counseling Points

- Tolerance to CNS effects may develop quickly; sedation will no longer be troublesome after a few days
- Avoid use with other medications that cause sedation
- Can be used on an as-needed basis

Key Points

- Most commonly used as a sedative and antipruritic
- Sedation is the most common adverse reaction
- Hydroxyzine is a vesicant and should be administered as an IM injection only
- Use may be inappropriate in the elderly due to its sedative and anticholinergic effects

Promethazine

Brand Name

Phenergan

Generic Name

Promethazine

Rx

Dosage Forms

Tablet, syrup, suppository, injection

Usage

Antiemetic, motion sickness, treatment of allergic conditions, sedation, adjunct for pain

Pregnancy Category C

Dosing

- Oral, rectal, injection:
  - Children > 2 years of age:
    - Use with caution at the lowest effective dose
    - 0.1–1 mg/kg/dose every 6 hours
    - Maximum: 25–50 mg/dose (varies based on indication)
  - Adults:
    - 25–50 mg at bedtime *or*
    - 12.5–25 mg every 4 to 8 hours, if needed
    - Maximum dose: 100 mg every 24 hours

Adverse Reactions: Rare/Severe/Important

Photosensitivity, blood dyscrasias, extrapyramidal symptoms, neuroleptic malignant syndrome, injection-site reactions (IM is the preferred route of parenteral administration; IV administration may cause severe tissue damage and is not recommended)

Major Drug Interactions

Drugs Affecting Promethazine

- Fluoxetine and paroxetine are CYP2D6 inhibitors that may lead to increased concentrations of promethazine
- Carbamazepine, phenobarbital, efavirenz, rifampin, and ritonavir are 2B6 inducers, which may lead to decreased concentrations of promethazine

Contraindications

Allergy to phenothiazines, children <2 years of age, intra-arterial or SUB-Q administration

Counseling Points

- Tolerance to CNS effects may develop quickly; sedation will no longer be troublesome after a few days
- Take with food, water, or milk to decrease GI upset
- For motion sickness, take 30 minutes to 1 hour before traveling
- Use sugarless gum or candy, ice, or saliva substitute to decrease dry mouth

Key Points

- **Black Box Warnings:**
  - Do not use in children younger than 2 years of age due to risk of fatal respiratory depression
  - Risk of severe tissue damage or gangrene with injectable formulation, subcutaneous route is contraindicated, avoid intravenous injection, if possible. The preferred route of the injectable formulation is deep intramuscular injection.
- Most commonly used for motion sickness or as an antiemetic but may be used for allergic reactions
- Promethazine is available in multiple dosage forms
- Use with caution in children > 2 years of age. Use the lowest effective dose and avoid with other CNS/respiratory depressant medications.

ANTIHISTAMINES, SECOND GENERATION, NONSEDATING

Introduction

The second-generation antihistamines are used for allergic rhinitis and urticaria. They are used to treat these chronic conditions due to the low risk of adverse events. These agents are more commonly used than the first-generation antihistamines because of the decreased risk of sedation. Sedation is most common with cetirizine. All of these agents are available in combination with pseudoephedrine. The combination products should not be used in patients <12 years of age.

Mechanism of Action for the Drug Class

These agents reversibly, competitively antagonize H1 receptors peripherally, blocking the increased capillary permeability (edema/wheel formation) and itching caused by histamine release. They do not cross the blood–brain barrier, resulting in reduced sedation.

Usage for the Drug Class

Allergic rhinitis, chronic urticaria

Adverse Reactions for the Drug Class: Most Common

Dizziness, dyspepsia, headache, nausea, xerostomia

Adverse Reactions for the Drug Class: Rare/Severe/Important

Rash

Members of the Drug Class

In this section: Fexofenadine, loratadine, cetirizine, levocetirizine

Others: Desloratadine, acrivastine (available with pseudoephedrine only)

◉ Fexofenadine

Brand Names

Allegra Allergy, Allegra Allergy Children's, Allegra 24-HR, Allegra D 12 hour (with pseudoephedrine), Allegra D 24 hour (with pseudoephedrine)

Generic Name

Fexofenadine

OTC

Dosage Forms

Tablet, extended-release tablet, oral disintegrating tablet (ODT; contains phenylalanine), oral suspension

Pregnancy Category

Limited information is available but does not appear to cause major malformations. Other second-generation antihistamines are preferred.

Dosing

- Children:
  - Combination product with pseudoephedrine should not be used in children < 12 years of age
  - 2 to 11 years:
    - 30 mg twice daily
    - Maximum dose: 30 mg twice daily
  - > 12 years of age:
    - 60 mg twice daily or 180 mg once daily
    - Maximum dose: 60 mg PO twice daily or 180 mg once daily
  - Renal dosage adjustment: If CrCl < 80 ml/min:
    - Six months to < 2 years of age: Initial dose of 15 mg once daily
    - Two to 11 years of age: Initial dose of 30 mg once daily
    - ≥ 12 years of age: Initial dose of 60 mg once daily
- Adults:
  - 60 mg twice daily or 180 mg once daily
  - Maximum dose: 60 mg twice daily or 180 mg once daily
  - Renal dosage adjustment: If CrCl 10–50 ml/min: Dose every 12 to 24 hours, CrCl < 10 ml/min or in hemodialysis or peritoneal dialysis: Dose every 24 hours

Major Drug Interactions

Drugs Affecting Fexofenadine

- Ketoconazole and erythromycin: May increase levels (without evidence of QT prolongation)
- Concomitant use of aluminum- or magnesium-containing antacids: Decreases bioavailability
- High-fat meals or fruit juice may decrease the bioavailability

Counseling Points

- Take at regular intervals
- Avoid aluminum- or magnesium-containing antacids
- Take with water
- Shake suspension before each use
- ODT should be taken on an empty stomach and should not be chewed
- Avoid use of other CNS depressants and alcohol; concomitant use may cause excess drowsiness

Key Points

- Available with pseudoephedrine for patients > 12 years of age
- Should not cause drowsiness
- Take with water (no juices)
- Patient should be counseled to shake suspension before use
- ODT should be taken on an empty stomach and should not be chewed

Loratadine

Brand Names

Alavert, Allergy Relief, Claritin, Claritin Children's, Claritin RediTabs, Claritin D 12 hour (with pseudoephedrine), Claritin D 24 hour (with pseudoephedrine)

Generic Name

Loratadine

OTC

Dosage Forms

Capsule, tablet, orally disintegrating tablet (ODT), chewable tablet, syrup

Pregnancy Category B

Maternal use has not been associated with fetal malformations and loratadine is considered to be the preferred antihistamine for the treatment of allergic rhinitis in pregnancy

Dosing

- Children:
  - 2 to 5 years of age:
    - 5 mg once daily
    - Maximum dose: 5 mg once daily
  - > 6 years of age:
    - 10 mg once daily
    - Maximum dose: 10 mg once daily or 5 mg twice daily (RediTabs)
- Adults:
  - 10 mg once daily
  - Maximum dose: 10 mg once daily
- Renal dosage adjustment: If CrCl 10–50 ml/min: Use every 24 to 48 hours, CrCl < 10 ml/min and with dialysis: Use every 48 hours
- Hepatic dosage adjustment: Use same dose and consider changing to every other day but there are no dosing recommendations in the manufacturer's labeling

Major Drug Interactions

None

Counseling Points

- Take at regular intervals
- RediTabs are rapidly disintegrating tablets that dissolve on the tongue. They can be administered with or without water.

Key Points

- Available with pseudoephedrine for patients > 12 years of age
- Should not cause drowsiness
- Preferred agent for the treatment of rhinitis in pregnant women

Levocetirizine

Brand Name
Xyzal

Generic Name
Levocetirizine

Rx and OTC

Dosage Forms
Tablet, oral solution

Pregnancy Category B

Dosing
- Children:
  - 6 months to 5 years of age: 1.25 mg once daily in the evening
  - 6 to 11 years of age: 2.5 mg once daily in the evening
  - ≥ 12 years: 5 mg once daily in the evening (patients may experience relief with 2.5 mg)
  - Renal dosage adjustment: Children 6 months to 11 years of age with renal impairment should not receive levocetirizine
- Adults:
  - 5 mg once daily in the evening (patients may experience relief with 2.5 mg)
  - Renal dosage adjustment:
    - CrCl = 50–80 ml/min: 2.5 mg once daily
    - CrCl = 30–50 ml/min: 2.5 mg once every other day
    - CrCl = 10–30 ml/min: 2.5 mg twice weekly (administer once every 3–4 days)
    - CrCl < 10 ml/min: Do not use levocetirizine
    - Hemodialysis: Do not use levocetirizine, as it is not dialyzable

Adverse Reactions: Rare/Severe/Important
Somnolence, fatigue

Major Drug Interactions
May have interactions similar to cetirizine

Drugs Affecting Levocetirizine
- CNS depressants may cause a possible additive effect
- Ritonavir may cause an increase in half-life and decrease clearance

Counseling Point
May cause drowsiness or dizziness; observe caution when driving and avoid using with alcohol or other medications that cause sedation

Key Points
- Levocetirizine is the R-enantiomer of cetirizine
- Somnolence similar to cetirizine may occur
- Should be adjusted in renal impairment and should not be used in children with renal impairment

Cetirizine

Brand Names
Zyrtec Allergy, Zyrtec Allergy Children's All Day Allergy, All Day Allergy Children's, Zyrtec-D Allergy & Congestion (with pseudoephedrine)

Generic Name
Cetirizine

OTC

Dosage Forms
Capsule, tablet, syrup, chewable tablet, orally disintegrating tablet

Pregnancy Category
Maternal use has not been associated with fetal malformations. Cetirizine is considered a preferred antihistamine for the treatment of rhinitis in pregnant women.

Dosing
- Children:
  - 6 to 12 months:
    - 2.5 mg once daily
    - Maximum dose: 2.5 mg once daily
  - 12 to 23 months:
    - 2.5 mg once daily
    - Maximum dose: 2.5 mg twice daily
  - 2 to 5 years:
    - 2.5 mg once daily
    - Maximum dose: 5 mg once daily *or* 2.5 mg twice daily
  - > 6 years:
    - 5–10 mg once daily
    - Maximum dose: 10 mg once daily
  - Renal dosage adjustment:
    - ≥ 6 years:
      - CrCl = 11–31 ml/min or hemodialysis: 5 mg once daily
      - CrCl < 11 ml/min, not on dialysis: Cetirizine use not recommended

Adverse Reactions: Rare/Severe/Important
None

Major Drug Interactions
Drugs Affecting Cetirizine
- Ritonavir: May increase concentration and half-life
- Theophylline ≥ 400 mg: May decrease clearance
- Alcohol or CNS depressants: Avoid concomitant use; additional decrease in mental alertness may occur

Counseling Point

May cause drowsiness or dizziness; observe caution when driving or taking other medications that cause somnolence; avoid drinking alcohol while on this medication

Key Points

- Causes more drowsiness than other agents in class
- Available with pseudoephedrine for patients >12 years of age
- Needs dose adjustment in renal impairment

ANTITUSSIVE

Introduction

Antitussives are used in the treatment of nonproductive cough. Benzonatate is used for acute and chronic cough. Benzonatate is chemically related to anesthetic agents in the para-amino-benzoic acid class (e.g., procaine, tetracaine). Sedation and GI upset are the most common side effects seen with these agents. Benzonatate capsules should not be crushed or chewed.

Mechanism of Action for the Drug Class

Benzonatate is a procaine derivative that suppresses cough through peripheral action, anesthetizing the stretch or cough receptors of vagal afferent fibers, which decreases the cough reflex.

Members of the Drug Class

In this section: Benzonatate
Others: Carbetapentane (note that codeine, dextromethorphan, and hydrocodone are covered in the Combination Cough/Cold Products section)

◉ Benzonatate

Brand Name

Tessalon Perles

Generic Name

Benzonatate

Rx

Dosage Form

Capsule

Usage

Symptomatic relief of nonproductive cough

Pregnancy Category C

Dosing

- Adults and children > 10 years:
  - Usual dose (age >10 years): 100–200 mg 3 times a day, as needed
  - Maximum dose (age >10 years): 600 mg every 24 hours

Adverse Reactions: Most Common

Sedation, GI upset, constipation, drowsiness, dizziness, headache, confusion

Adverse Reactions: Rare/Severe/Important

Oropharyngeal anesthesia, if capsules are chewed or dissolved in mouth; burning sensation in eyes; hypersensitivity reactions (including bronchospasm, laryngospasm, cardiovascular collapse) related to local anesthesia from sucking or chewing the capsules; hallucinations

Contraindication

Patients with a history of a prior reaction to related anesthetic agents (e.g., tetracaine/procaine)

Major Drug Interactions

Drugs Affecting Benzonatate

Alcohol and CNS depressants: Potentiate drowsiness

Counseling Points

- Swallow whole; do not chew or dissolve capsule in mouth
- Report any persistent CNS changes or burning/numbness in mouth or chest to your healthcare provider
- Accidental ingestion and fatal overdose reported in children < 10 years of age. As with all medications, keep out of reach of children.

Key Points

- Most commonly used for cough
- Do not break or puncture capsule. Swallow whole.
- Patients should discontinue use if hallucinations or burning in chest occur

BETA-2 AGONIST AND ANTICHOLINERGIC COMBINATION INHALER

Introduction

The primary use of these combination inhalers is for the chronic treatment of COPD when bronchospasms are still occurring despite treatment with a single bronchodilator. Ipratropium and albuterol are short-acting bronchodilators also used for the treatment of bronchospasms or exacerbations associated with COPD and asthma. Ipratropium and albuterol are primarily used on an as-needed basis for the treatment of bronchospasm associated with chronic COPD. The other inhaled agents in this class are the combination of long-acting anticholinergics and long-acting beta-2 agonists used for the chronic treatment of COPD. The most common adverse events associated with these agents are dry mouth and nervousness. Each agent uses a different inhalation device and patient counseling is an important component of prescribing these agents.

Mechanism of Action for the Drug Class

The use of both drugs with different mechanisms of action may have a synergistic bronchodilator effect.

Inhaled Anticholinergics

The drug class appears to produce bronchodilation by blocking acetylcholine at muscarinic receptors, therefore, blocking the direct constrictor effects of acetylcholine on bronchial smooth muscle. Inhaled anticholinergic agents block all muscarinic receptor subtypes (M1 to M5). In the airways, they exhibit pharmacologic activity by inhibiting the M3 receptors in the smooth muscle, causing bronchodilation. Tiotropium and umeclidinium are long-acting antimuscarinic agents that inhibit the action of acetylcholine at type 3 muscarinic receptors (M_3) in bronchial smooth muscle and slowly dissociate from this receptor subtype, leading to the long-acting effect.

Beta-2 Agonists

Activation of the beta-2 receptors results in increases of cyclic AMP, which stimulates relaxation of the smooth airway. Beta-2 agonists also produce bronchodilation by inhibiting the release of inflammatory mediators from mast cells and preventing microvascular leakage into the bronchial mucosa.

Members of the Drug Class

In this section: Albuterol and ipratropium, glycopyrrolate and formoterol, indacaterol and glycopyrrolate, tiotropium and olodaterol, umeclidinium, and vilanterol
Others: None

Adverse Reactions: Most Common

- Anticholinergics: Cough, dry mouth, dyspepsia, dizziness, blurred vision, headache, sore throat, taste perversion
- Beta-Agonists: Nervousness, palpitations, tachycardia, tremor, headache, CNS stimulation, cough, nausea, throat irritation, pharyngitis, respiratory infection

Adverse Reactions for the Drug Class: Rare/Severe/Important

- Anticholinergics: Paradoxical bronchospasms; worsening of narrow-angle glaucoma/mydriasis; increased intraocular pressure (especially if sprayed into eyes); worsening of urinary retention
- Beta-Agonists: Paradoxical bronchospasms, hyperglycemia, hypokalemia, hypertension, QTc prolongation (with high doses); use caution in patients with cardiac arrhythmias, uncontrolled hypertension, uncontrolled hyperthyroidism, or diagnosed or suspected pheochromocytoma because these agents may exacerbate the condition

Major Drug Interactions for the Drug Class

Drugs Affecting Beta-Agonists

- Nonselective beta blockers (ophthalmic and systemic): May blunt the bronchodilating effects causing bronchospasm
- Nonpotassium–sparing diuretics: May lead to hypokalemia when used with high doses of beta-agonists

Beta-Agonists' Effect on Other Drugs

- None

Drugs Affecting Anticholinergics

- Other anticholinergics or drugs that have anticholinergic properties: May potentiate effects

◉ Albuterol and Ipratropium

Brand Names

Combivent, Respimat

Generic Names

Albuterol and ipratropium

Rx

Dosage Forms

Solution for oral inhalation, solution for nebulization

Usage

Bronchospasms associated with COPD, acute asthma exacerbations

Pregnancy Category C

Dosing

- Combivent Respimat:
  - One oral inhalation four times a day; can be used on an as-needed basis
  - Maximum dose: Six puffs every 24 hours (may be used more frequently in the treatment of acute asthma and COPD exacerbations)
- Solution for nebulization: 3 ml nebulized and inhaled orally every 4 to 6 hours (may be used more frequently in the treatment of acute asthma and COPD exacerbations)

Contraindication

None

Counseling Points

- Use proper administration technique:
  - Combivent Respimat:
    1. Before using the inhaler for the first time, the Combivent Respimat cartridge must be inserted into the Combivent Respimat inhaler and then primed
    2. Priming is necessary when the inhaler is used for the first time or when the inhaler has not been used for > 3 days
       a. When using the unit for the first time, actuate the inhaler toward the ground until an aerosol cloud is visible and then repeat the process 3 times
       b. If not used for > 3 days, actuate the inhaler once to prepare the inhaler for use
       c. If not used > 21 days, actuate the inhaler until an aerosol cloud is visible and then repeat the process 3 times to prepare the inhaler for use
    3. Hold the Combivent Respimat inhaler upright with the orange cap closed to avoid accidental release of dose
    4. Turn the clear base in the direction of the white arrows on the label until it clicks (half a turn) and flip the orange cap until it snaps fully open
    5. Breathe out slowly and fully and then close your lips around the end of the mouthpiece without covering the air vents. Point the Combivent Respimat inhaler to the back of your throat.
    6. While taking in a slow, deep breath through your mouth, press the dose release button and continue to breathe in slowly for as long as you can. Hold your breath for 10 seconds or for as long as is comfortable.
    7. Close the orange cap until you use your Combivent Respimat inhaler again
  - If using more than the prescribed amount, contact your healthcare provider
  - Avoid contact with eyes
  - Use with the proper spacing device
  - Protect the nebulization solution from light

Key Points

- Commonly used in COPD or the treatment of acute exacerbations of COPD and asthma
- Most common adverse effects are dry mouth and nervousness
- Inform patients with glaucoma or urinary retention to report worsening symptoms after use of this agent

Formoterol and Glycopyrrolate

Brand Names

Bevespi Aerosphere

Generic Names

Formoterol and Glycopyrrolate

Rx

Dosage Forms

Aerosol for oral inhalation

Usage

Maintenance treatment for COPD

Pregnancy Category C

Dosing

Glycopyrrolate 9 μg and formoterol fumarate dihydrate 4.8 μg per inhalation, 2 puffs inhaled orally 2 times a day (maximum: 4 puffs/day)

Contraindications

Monotherapy in patients with asthma (i.e., without use of a long-term asthma control medication)

Counseling Points

- Use proper administration technique:
  - Bevespi Aerosphere
    1. Shake inhaler for at least 10 seconds and remove the dust cap
    2. Prior to use, inhaler must be primed by releasing four test sprays into the air (away from face and eyes), shake well before each spray
    3. Inhaler must be reprimed if not used > 7 days by releasing 2 sprays into the air. Shake well before each use
    4. When dose is ready to be administered, breathe in slowly through the mouth and press the

dose-release button; continue to breathe in slowly as long as possible, then hold breath for 10 seconds or for as long as comfortable; repeat for second inhalation
5. Clean inhaler (remove canister out of actuator) one time each week by running warm water through the actuator and allow to air dry
6. Reprime the inhaler after each cleaning by releasing two sprays into the air.

Key Points

- **Black Box Warnings**:
  - Asthma-related deaths: [U.S. Boxed Warning]: Long-acting beta-2-agonists (LABAs) increase the risk of asthma-related death
  - Most common adverse effects are dry mouth and nervousness
  - Inform patients with glaucoma or urinary retention to report worsening symptoms after use of this agent

Indacaterol and Glycopyrrolate

Brand Names

Utibron Neohaler

Generic Names

Indacaterol and Glycopyrrolate

Rx

Dosage Form

Capsule for oral inhalation
Each capsule contains 27.5 µg of Indacaterol and 15.6 µg of glycopyrrolate delivered via a special dry powder inhaler device (Neohaler) for oral inhalation only

Usage

Maintenance treatment for COPD

Pregnancy Category C

Dosing

- 1 capsule (indacaterol 27.5 µg/glycopyrrolate 15.6 µg) inhaled twice daily (maximum: 2 capsules/day)

Contraindications

- Monotherapy in patients with asthma (i.e., without use of a long-term asthma control medication
- Utibron Neohaler contains lactose. Avoid use in patients with severe hypersensitivity to milk proteins.

Counseling Points

- Should not be used to treat acute bronchospasms
- Capsule is for inhalation only via the Neohaler device; do not swallow capsules
- Use proper administration technique via the Neohaler inhaler device:
  1. Pull off cap to expose mouthpiece
  2. Hold the base of the inhaler firmly and tilt the mouthpiece to open the inhaler
  3. Remove capsule from blister pack. Do not open capsule.
  4. Insert capsule into capsule chamber. It does not matter which end of the capsule you put in the chamber.
  5. Close the mouthpiece until you hear a "click"
  6. Hold the inhaler upright and pierce the capsule by firmly pressing together both side buttons at the same time (do this only once) a click sound should be heard when capsule is being pierced
  7. Release the side buttons fully
  8. Breathe out completely. Do not exhale into the mouthpiece.
  9. Breathe in rapidly, steadily, and deeply so you hear or feel the capsule vibrate
  10. Hold your breath for at least 5 to 10 seconds or as long as you comfortably can while taking the inhaler out of your mouth
  11. To get the full dose of the medication, you must breathe out completely and repeat steps 8 through 10

Key Points

- **Black Box Warning**:
  - Asthma-related deaths: [U.S. Boxed Warning]: Long-acting beta-2-agonists (LABAs) increase the risk of asthma-related death
- Capsule should be inhaled via Neohaler only and should not be swallowed
- Most common adverse effects are dry mouth and nervousness
- Inform patients with glaucoma or urinary retention to report worsening symptoms after use of this agent

Olodaterol and Tiotropium

Brand Names

Stiolto Respimat

Generic Names

Olodaterol and tiotropium

Rx

Dosage Form

Aerosol Solution for Inhalation
Tiotropium 2.5 µg and olodaterol 2.5 µg per actuation

Usage
Maintenance treatment for COPD

Pregnancy Category C

Dosing
Maximum of 2 inhalations once per day

Contraindications
Monotherapy in patients with asthma without use of a long-term asthma control medication

Counseling Points
- Do not use for acute attacks
- Use proper administration technique:
  1. Shake the inhaler well immediately before each use. Then remove the cap from the mouthpiece.
  2. Prime the inhaler before using it for the first time and when the inhaler has not been used for > 21 days. Prime by releasing 4 sprays into the air away from your face. If the inhaler has not been used for > 3 days (but ≤ 21 days), prime once before use.
  3. When dose is ready to be administered, breathe in slowly through the mouth and press the dose release button; continue to breathe in slowly as long as possible, then hold breath for 10 seconds or for as long as comfortable
  4. Repeat for second inhalation
  5. Breathe out deeply

Key Points
- **Black Box Warning**:
  - Asthma-related deaths: [U.S. Boxed Warning]: Long-acting beta-2-agonists (LABAs) increase the risk of asthma-related death.
  - Should not be used for acute bronchospasm

◉ Vilanterol and Umeclidinium

Brand Names
Anoro Ellipta

Generic Names
Vilanterol and Umeclidinium

Rx

Dosage Form
Aerosol Powder for Inhalation
Umeclidinium 62.5 µg and vilanterol 25 µg per inhalation

Usage
Maintenance treatment for COPD

Pregnancy Category C

Dosing
Maximum of 1 inhalation once per day

Contraindications
Monotherapy in patients with asthma without use of a long-term asthma control medication
Anoro Ellipta contains lactose. Avoid use in patients with severe hypersensitivity to milk proteins.

Counseling Points
- Do not use for acute attacks
- Should not be used to treat acute bronchospasms
- Only open inhaler cover when ready for administration; opening and closing the cover without inhaling the medicine will cause a dose to be lost (the dose will be held in the inhaler, but it will no longer be available to be inhaled); it is not possible to accidentally take a double dose or an extra dose in one inhalation
- The dose counter tells you how many doses are left
- Discard inhaler 6 weeks after opening the foil tray or after the labeled number of inhalations have reached zero (whichever occurs first)
- Directions for proper administration technique:

Counseling Points
- The dose indicator tells you how many doses are left
- If you open and close the cover without inhaling the medicine, you will lose the dose
- Discard inhaler 6 weeks after opening the foil tray or after the labeled number of inhalations have reached zero (whichever comes first)
- Use proper administration technique:
  1. When you are ready to inhale a dose, open the cover of the inhaler, slide the cover down to expose the mouthpiece. You should hear a "click." The counter will count down by one number. You do not need to shake this kind of inhaler.
  2. Exhale fully, do not breathe out into the mouthpiece
  3. Put the mouthpiece between your lips, and close your lips firmly around it
  4. Take one long, steady, deep breath in through your mouth
  5. Do not block the air vent with your fingers
  6. Remove the inhaler from your mouth
  7. Hold your breath for 3 to 4 seconds (or as long as is comfortable)
  8. Breathe out slowly and gently
  9. Close the lid of the inhaler

Key Points
- **Black Box Warning:**
  - Asthma-related deaths: [U.S. Boxed Warning]: Long-acting beta-2-agonists (LABAs) increase the risk of asthma-related death
- Should not be used for acute bronchospasm

BETA-2 AGONIST AND CORTICOSTEROID COMBINATION INHALER

Introduction

Long-acting beta-2 agonist/corticosteroid inhaler combinations are used for the chronic treatment of asthma. These agents are also used in patients COPD at high risk of having an exacerbation. Different strengths of corticosteroids are available, depending on the patient's asthma severity. Moderate-to-high-dose corticosteroid combinations are used in the treatment of COPD. It is important to counsel patients on the proper use of the inhaler and to rinse their mouth with water after each use. Patients should also be informed that these inhalers should not be used to treat acute bronchospasm or shortness of breath and that these agents need to be used regularly to achieve maximal effect. Coughing, dry mouth, and oral candidiasis are the most common adverse effects seen with these agents.

Mechanism of Action for the Drug Class

Beta-2 Agonist

Activation of the beta-2 receptors results in increases of cyclic AMP, which stimulates relaxation of the smooth airway. Beta-2 agonists also produce bronchodilation by inhibiting the release of inflammatory mediators from mast cells and preventing microvascular leakage into the bronchial mucosa.

Inhaled Corticosteroids

Inhaled corticosteroids do not directly affect airway smooth muscle. Inhaled corticosteroids decrease the number of inflammatory cells (basophils, mast cells, neutrophils, eosinophils, macrophages, and lymphocytes) and inflammatory mediators (histamines, leukotrienes, and cytokines), leading to decreased airway edema and hyper-responsiveness of smooth muscle. Steroids also inhibit mucus secretion in the airways.

Usage for the Drug Class

Maintenance Treatment of asthma and COPD

Adverse Reactions for the Drug Class: Most Common

- Corticosteroids: Hoarseness, pharyngitis, dry mouth, coughing, headache, hypokalemia, oral candidiasis, palpitations, tachycardia, tremor
- Beta-Agonists: Nervousness, palpitations, tachycardia, tremor, headache, CNS stimulation, cough, nausea, throat irritation, pharyngitis, respiratory infection

Adverse Reactions for the Drug Class: Rare/Severe/Important

- Corticosteroids: Adrenal insufficiency, upper respiratory tract infections, pneumonia, decreases in bone mineral density, possible asthma-related death
- Beta-Agonists: Paradoxical bronchospasms, hyperglycemia, hypokalemia, hypertension, QTc prolongation (with high doses); use caution in patients with cardiac arrhythmias, uncontrolled hypertension, uncontrolled hyperthyroidism, or diagnosed or suspected pheochromocytoma because these agents may exacerbate the condition

Major Drug Interactions for the Drug Class

Drugs Affecting Beta-Agonists

- Nonselective beta blockers (ophthalmic and systemic): May blunt the bronchodilating effects causing bronchospasm
- Nonpotassium sparing diuretics: May lead to hypokalemia when used with high doses of beta-agonists

Beta-Agonists' Effect on Other Drugs

- None

Counseling Points for the Drug Class

- Rinse mouth with water after each use
- Use every day
- Do not use for acute attacks. You must have a rescue inhaler available for breakthrough attacks.
- Use proper administration technique
- Do not discontinue abruptly

Key Points for the Drug Class

- **Black Box Warning:**
  - Long-acting beta-2 agonists may increase the risk of asthma-related deaths and hospitalizations. When treating asthma, long-acting beta-2 agonists should only be used when therapy with an inhaled corticosteroid is insufficient to manage asthma. Patients should be reassessed to determine if the long-acting beta-2 agonist can be discontinued once asthma control is maintained.
- Used in the chronic treatment of COPD and asthma
- Should not be used for treatment of exacerbations
- Use as prescribed to see maximal benefit
- It may take 1 to 4 weeks to see maximal benefit
- Rinse mouth with each use to avoid oral candidiasis

Members of the Drug Class

In this section: Fluticasone and salmeterol, budesonide and formoterol, Fluticasone and vilanterol, Mometasone and formoterol
Others: None

◉ Fluticasone and Salmeterol

Brand Names

Advair, Advair HFA

Generic Name

Fluticasone and salmeterol

Rx

Dosage Forms

Powder for inhalation via Diskus inhaler, CFC-free inhalation aerosol

Pregnancy Category C

Dosing

- Diskus: Available in 100 µg/50 µg, 250 µg/50 µg, 500 µg/50 µg
  - Children, asthma:
    - 4 to 11 years: Initial dose is fluticasone 100 µg/salmeterol 50 µg, 1 inhalation orally every 12 hours (this is maximum dose)
    - >12 years: Initial dose is fluticasone 100 µg/salmeterol 50 µg, 1 puff inhaled orally every 12 hours
  - Adults:
    - Asthma:
      - Initial dose: Fluticasone 100 µg/salmeterol 50 µg, 1 puff inhaled orally every 12 hours
      - Dosage adjustment: Titrate to the most effective dose that controls symptoms
      - Maximum dose: Fluticasone 500 µg/salmeterol 50 µg (2 inhalations daily)
    - COPD: Fluticasone 250 µg/salmeterol 50 µg, one puff inhaled orally every 12 hours (this is also the maximum dose in COPD)
- Inhalation aerosol (HFA): Available in 45 µg/21µg, 115 µg/21 µg, 230 µg/21 µg
  - 2 puffs inhaled orally every 12 hours
  - Maximum dose: Fluticasone 230 µg/salmeterol 21 µg per inhalation (four inhalations/day)

Major Drug Interactions

Drugs Affecting Fluticasone

- Strong CYP3A4 inhibitors: Increase concentrations of fluticasone and which may cause reduced levels of cortisol
- Protease inhibitors: Decrease metabolism, which can increase fluticasone concentrations; reports of Cushing's syndrome developing from this combination have been found in the literature. It is not recommended to use together.

Drugs Affecting Salmeterol

- Inhibitors of CYP3A4: Increase salmeterol concentrations, possibly causing palpitations, tachycardia and QTc prolongation

Contraindication

Advair Diskus contains lactose. Avoid use in patients with severe hypersensitivity to milk proteins.

Counseling Points

- The dose indicator tells you how many doses are left
  Use proper administration technique:
  - Diskus:
    1. Activate the dry powder inhaler by sliding the activator. Every time the lever is pushed back, a dose is ready to be inhaled. Do not close or tilt the Diskus after the lever is pushed back.
    2. Breathe out deeply
    3. Inhale the powder contents completely
  - Inhalation aerosol (HFA):
    1. Shake well for 5 seconds before each spray. Prime with 4 test sprays (into air and away from face) before using for the first time. If canister is dropped or not used for >4 weeks, prime with 2 sprays.
    2. Take the cap off the mouthpiece and shake the inhaler for 5 seconds
    3. Put the mouthpiece in your mouth and seal lips around it
    4. Push the top of the canister all the way down while you breathe in deeply and slowly through your mouth. Hold your breath for 10 seconds or as long as you can.
    5. Wait 30 seconds, shake inhaler for 5 seconds again, and repeat steps 3 and 4

Fluticasone and Vilanterol

Brand Names

Breo Ellipta

Generic Name

Fluticasone and vilanterol

Rx

Dosage Form

Powder for inhalation

Usage

Chronic maintenance of asthma, *maintenance treatment of COPD*

Pregnancy Category C

Dosing

- Adults:
  - Asthma:
    - Initial dose: Fluticasone 100 µg/vilanterol 25 µg, one inhalation orally once daily
    - Maximum dose: Fluticasone 200 µg/vilanterol 25µg, one inhalation orally once daily
  - COPD: Fluticasone 100 µg/vilanterol 25 µg, 1 inhalation orally once daily (this is also the maximum dose in COPD)

Major Drug Interactions

Drugs Affecting Fluticasone

- Ketoconazole or CYP3A4 inhibitors: Increase levels (clinical effect unknown)
- Protease inhibitors: Decrease metabolism; reports of Cushing's syndrome developing from this combination have been found in the literature

Contraindication

Breo Ellipta contains lactose. Avoid use in patients with severe hypersensitivity to milk proteins.

Counseling Points

- The dose indicator tells you how many doses are left
- If you open and close the cover without inhaling the medicine, you will lose the dose
- Discard inhaler 6 weeks after opening the foil tray or after the labeled number of inhalations have reached zero (whichever comes first)
- Use proper administration technique:
  1. When you are ready to inhale a dose, open the cover of the inhaler and slide the cover down to expose the mouthpiece. You should hear a "click." The counter will count down by one number. You do not need to shake this kind of inhaler.
  2. Exhale fully, do not breathe out into the mouthpiece
  3. Put the mouthpiece between your lips, and close your lips firmly around it
  4. Take one long, steady, deep breath in through your mouth
  5. Do not block the air vent with your fingers
  6. Remove the inhaler from your mouth
  7. Hold your breath for 3 to 4 seconds (or as long as is comfortable)
  8. Breathe out slowly and gently
  9. Close the lid of the inhaler

Budesonide and Formoterol

Brand Name

Symbicort

Generic Name

Budesonide and formoterol

Rx

Dosage Form

Metered-dose inhaler (MDI)

Pregnancy Category C

Dosing

- Children 6 to 12 years for asthma: Budesonide/formoterol 80/4.5: 2 inhalations by mouth twice daily
- Children > 12 years of age and adults for asthma: Budesonide/formoterol 80/4.5 or 160/4.5: 2 inhalations by mouth twice daily (starting dose, depending on asthma severity)
- Maximum dose: 4 inhalations per day
- COPD: Budesonide/formoterol 160/4.5: 2 inhalations twice daily

Major Drug Interactions

Drugs Affecting Budesonide

Strong CYP3A4 inhibitors: May decrease the metabolism of budesonide leading to increased systemic concentrations

Counseling Point

Counsel on proper inhalation technique. Prior to first use, the inhaler must be primed by releasing two test sprays into the air; shake well for 5 seconds before each spray. Inhaler must be reprimed if not used for >7 days or if it has been dropped. Shake well for 5 seconds before each use.

Mometasone/Formoterol

Brand Names

Dulera

Generic Name

Mometasone and formoterol

Rx

Dosage Forms

Aerosol for oral inhalation

Usage

Chronic maintenance of asthma, maintenance treatment of COPD

Pregnancy Category

Animal reproduction studies have not been conducted with this combination. Individual components: Formoterol is pregnancy category C and mometasone is pregnancy category C

Dosing

- Children > 12 years of age and adults:
  - Asthma:
    - Initial dose (based on previous inhaled corticosteroid dose therapy): Mometasone 100 µg/formoterol 5 µg, 2 puffs inhaled orally twice daily
    - Dosage adjustment: Titrate to the most effective dose that controls symptoms *(following 2 weeks of therapy)*
    - Maximum dose: Mometasone 800 µg/formoterol 20 µg (number of inhalations/day, depends on the strength of the metered dose inhaler)

- COPD:
  - Initial dose: Mometasone 100 µg/formoterol 5 µg, two puffs inhaled orally twice daily
  - Maximum: Mometasone 200 µg/formoterol 5 µg, two puffs inhaled orally twice daily

Major Drug Interactions

None

Contraindication

None

Counseling Points

- The dose indicator tells you how many doses are left
- Use proper administration technique:
  1. Shake well for 5 seconds before each spray. Prime with four test sprays (into air and away from face) before using for the first time. If canister is dropped or not used for > 5 days, prime with two sprays.
  2. Take the cap off the mouthpiece and shake the inhaler for 5 seconds
  3. Put the mouthpiece in your mouth and seal lips around it
  4. Push the top of the canister all the way down while you breathe in deeply and slowly through your mouth. Hold your breath for 10 seconds or as long as you can.
  5. Wait 30 seconds, shake inhaler for 5 seconds again, and repeat steps 3 and 4

BETA-2 AGONISTS, INHALED

Introduction

The inhaled beta-2 agonists are primarily used for the treatment and prevention of bronchospasms in patients with obstructive airway disease (asthma and COPD). They can be used chronically or in the treatment of an exacerbation of the disease. Short-acting beta-2 agonists, albuterol and levalbuterol, are commonly used on an as-needed basis for symptomatic control or for the treatment of an acute exacerbation. The inhaled preparation of albuterol is used more commonly than the systemic preparations. The tablets and syrup are associated with an increased frequency of adverse reactions and are no longer recommended for the treatment of asthma. Long-acting agents are used every day for the chronic management and not on an as-needed basis. Patients should be counseled on the proper use of these medications. The most common adverse reactions are palpitations, tachycardia, and tremor. Adverse reactions are more common with the short-acting beta-2 agonists than with the long-acting agents.

Mechanism of Action for the Drug Class

Activation of the beta-2 receptors results in increases of cyclic AMP, which stimulates relaxation of the smooth airway. Beta-2 agonists also produce bronchodilation by inhibiting the release of inflammatory mediators from mast cells and preventing microvascular leakage into the bronchial mucosa.

Adverse Reactions for the Drug Class: Most Common

Nervousness, palpitations, tachycardia, tremor, headache, CNS stimulation, cough, nausea, throat irritation, pharyngitis, respiratory infection

Adverse Reactions for the Drug Class: Rare/Severe/Important

Paradoxical bronchospasms, hyperglycemia, hypokalemia, hypertension, QTc prolongation (with high doses); use caution in patients with cardiac arrhythmias, uncontrolled hypertension, uncontrolled hyperthyroidism, or diagnosed or suspected pheochromocytoma because these agents may exacerbate the condition

Major Drug Interactions for the Drug Class

Drugs Affecting Beta-Agonists

- Nonselective beta blockers (ophthalmic and systemic): May blunt the bronchodilating effects, causing bronchospasm
- Nonpotassium sparing diuretics: May lead to hypokalemia when used with high doses of beta-agonists

Beta-Agonists' Effect on Other Drugs

- None

Members of the Drug Class

In this section: Albuterol, formoterol, indacaterol, levalbuterol, olodaterol, salmeterol
Others: Arformoterol

Key Points for the Drug Class

- **Black Box Warning:**
  - Long-acting beta-2 agonists may increase the risk of asthma-related deaths and hospitalizations. When treating asthma, long-acting beta-2 agonists should only be used when therapy with an inhaled corticosteroid is insufficient to manage asthma. Patients should be reassessed to determine if the

long-acting beta-2 agonist can be discontinued once asthma control is maintained.
- Adverse effects of tachycardia, palpitations, tremor, and nervousness are more common with short-acting beta-2 agonists than with long-acting agents

Albuterol

Brand Names
Ventolin HFA, Proventil HFA, ProAir HFA, ProAir RespiClick

Generic Name
Albuterol

Rx Only

Dosage Forms
HFA inhaler, breath-activated aerosol powder, nebulizer solution, tablet, extended-release tablet, syrup

Usage
Relief and prevention of bronchospasm associated with asthma and COPD, acute attacks of bronchospasm, exercise-induced bronchospasm, treatment of acute hyperkalemia

Pregnancy Category C

Dosing
- Relief and prevention of bronchospasm:
  - HFA: Children age >4 years and adults should take 2 puffs inhaled orally every 6 hours as needed (additional inhalatins may be necessary if inadequate relief: In exacerbations, may use 4 to 8 inhalations every 20 minutes for 3 doses, then every 1 to 4 hours, as needed)
  - Nebulizer solution:
    - Children:
      - 2 to 12 years: 0.63–1.25 mg inhaled via nebulizer every 4 to 6 hours as needed (up to 2.5 mg/dose has been used) [additional inhalations may be necessary if inadequate relief: In exacerbations, may use 0.15 mg/kg (min 2.5 mg) every 20 minutes for 3 doses, then every 1 to 4 hours as needed
      - >12 years: See adult dosing
    - Adults: 1.25–2.5 mg inhaled via nebulizer every 4 to 8 hours, as needed (up to 5 mg/dose has been used)
  - Oral tablets, syrup:
    - Children:
      - 2 to 6 years:
        - 0.1–0.2 mg/kg/dose every 8 hours
        - Maximum dose: 12 mg every 24 hours
      - 6 to 12 years:
        - 2 mg orally every 6 to 8 hours
        - Maximum dose: 24 mg every 24 hours
      - >12 years: See adult dosing
    - Adults:
      - 2–4 mg orally every 6 to 8 hours
      - Maximum dose: 32 mg every 24 hours
  - Extended-release tablets:
    - Children:
      - 6 to 12 years:
        - 4 mg orally every 12 hours
        - Maximum dose: 24 mg every 24 hours
      - >12 years: See adult dosing
    - Adults:
      - 4–8 mg orally every 12 hours
      - Maximum dose: 32 mg/24 hours
- Exercise-induced asthma:
  - Children ≤ 4 years: 1 to 2 inhalations 5 minutes prior to exercise
  - Children >4 years and adults: 2 inhalations 5 minutes prior to exercise

Contraindications
Severe hypersensitivity to milk proteins (powder for inhalation only—ProAir RespiClick)

Counseling Points
- Use proper administration technique:
  1. Shake the inhaler well immediately before each use. Then remove the cap from the mouthpiece.
  2. Prime the inhaler before using it for the first time and when the inhaler has not been used for >2 weeks. Prime by releasing 4 sprays into the air, away from your face.
  3. Breathe out fully from your mouth, expelling as much air from your lungs as possible. Place the mouthpiece fully into the mouth, holding the inhaler in its upright position and closing the lips around it.
  4. While breathing in deeply and slowly through the mouth, press the top of the metal canister with your index finger
  5. Hold your breath as long as possible, up to 10 seconds. Before breathing out, remove the inhaler from your mouth and release your finger from the canister.
  6. If your physician has prescribed additional puffs, wait 1 minute, shake the inhaler again, and repeat steps 3 to 5. Replace the cap after use.
- If using more than the prescribed amount, contact your healthcare provider
- If using more than 2 times a week and not on any anti-inflammatory inhalers, check with your healthcare provider
- Swallow extended-release tablets whole; do not crush or chew

Key Points

- Albuterol is a short-acting beta-2 selective agonist used for the treatment of acute symptomatic control of asthma and COPD
- The inhaled dosage forms are the most commonly recommended
- Oral tablets and syrup are not recommended for the immediate relief of bronchospasms or for the chronic treatment of asthma

◉ Formoterol

Brand Name

Perforomist Solution for Nebulization

Generic Name

Formoterol

Rx Only

Dosage Form

Solution for nebulization

Usage

Maintenance treatment of COPD

Pregnancy Category C

Dosing

- COPD:
- Solution for nebulization: 20 µg inhaled twice daily

Contraindications

Use as monotherapy in asthma

Counseling Points

- Do not use for acute attacks/symptoms of asthma/COPD
- Do not use more frequently than the recommended dose
- Remove unit-dose vial from foil pouch immediately before use. Solution does not require dilution prior to administration in nebulizer; do not mix other medications with formoterol solution.

Key Points

- Formoterol is a long-acting beta-2 agonist
- It should only be used in combination with inhaled corticosteroids in asthma
- Adverse effects are minimal compared with short-acting beta-2 agonists

◉ Indacaterol

Brand Name

Arcapta Neohaler

Generic Name

Indacaterol

Rx

Dosage Forms

Capsule for inhalation: Each capsule contains 75 µg powder, delivered via a special dry powder inhaler device (Neohaler) for oral inhalation only

Mechanism of Action

Indacaterol is a long-acting beta-2 agonist that produces bronchodilation by relaxing the smooth muscles of the bronchioles

Usage

Maintenance treatment of COPD

Pregnancy Category C

Dosing

One capsule (75 µg) inhaled once daily using Neohaler inhaler

Contraindications

- Use as monotherapy in the treatment of asthma
- Arcapta Neohaler contains lactose. Avoid use in patients with severe hypersensitivity to milk proteins.

Counseling Points

- Do not use for acute attacks
- Use proper administration technique via the Neohaler device:
  1. Pull off cap to expose mouthpiece.
  2. Hold the base of the inhaler firmly and tilt the mouthpiece to open the inhaler
  3. Remove capsule from blister pack. Do not open capsule.
  4. Insert capsule into capsule chamber. It does not matter which end of the capsule you put in the chamber.
  5. Close the mouthpiece until you hear a "click"
  6. Hold the inhaler upright and pierce the capsule by firmly pressing together both side buttons at the same time (do this only once); a click sound should be heard when capsule is being pierced
  7. Release the side buttons fully
  8. Breathe out completely. Do not exhale into the mouthpiece
  9. Breathe in rapidly, steadily, and deeply so you hear or feel the capsule vibrate
  10. Hold your breath for at least 5 to 10 seconds or as long as you comfortably can while taking the inhaler out of your mouth

11. To get the full dose of the medication, you must breathe out completely and repeat steps 8 through 10

Key Points

- **Black Box Warning:**
  - Asthma-related deaths: [U.S. Boxed Warning]: Long-acting beta-2 agonists (LABAs) increase the risk of asthma-related deaths
- Indacaterol is a long-acting beta-2 selective agonist
- Should only be used in combination with inhaled corticosteroids in asthma
- Should not be used for acute bronchospasm

Levalbuterol

Brand Names

Xopenex, Xopenex HFA

Generic Name

Levalbuterol

Rx Only

Dosage Forms

Metered dose inhaler (MDI), solution for nebulization

Usage

Treatment of bronchospasms in children and adults with asthma and adults with COPD

Pregnancy Category C

Dosing

- HFA: Children age >4 years and adults should take 2 puffs, inhaled by mouth every 4 to 6 hours, as needed
  - *Note:* May use 4 to 8 inhalations every 20 minutes up to 4 hours then every 1 to 4 hours, as needed for the treatment of acute exacerbations
- Solution for nebulization:
  - Children age ≤4 years: 0.31–1.25 mg inhaled by nebulizer every 4 to 6 hours, as needed
  - Children age 5 to 11 years: 0.31–0.63 mg inhaled via nebulizer every 8 hours, as needed
  - Children age ≥12 years and adults: 0.63–1.25 mg inhaled via nebulizer every 8 hours, as needed
  - *Note:* May use every 20 minutes for 3 doses then 2.5–5 mg every 1 to 4 hours, as needed for the treatment of acute exacerbations

Counseling Points

- Use proper administration technique:
  1. Shake the inhaler well immediately before each use. Then remove the cap from the mouthpiece.
  2. Prime the inhaler before using it for the first time and when the inhaler has not been used for > 2 weeks. Prime by releasing four sprays into the air, away from your face.
  3. Breathe out fully from your mouth, expelling as much air from your lungs as possible. Place the mouthpiece fully into the mouth, holding the inhaler in its upright position and closing the lips around it.
  4. While breathing in deeply and slowly through the mouth, press the top of the metal canister with your index finger
  5. Hold your breath for as long as possible, up to 10 seconds. Before breathing out, remove the inhaler from your mouth and release your finger from the canister.
  6. If your physician has prescribed additional puffs, wait 1 minute, shake the inhaler again, and repeat steps 3 through 5. Replace the cap after use.
- If using more than the prescribed amount, contact your healthcare provider
- If using more than two times a week and not on any anti-inflammatory inhalers, check with your healthcare provider

Key Points

- Levalbuterol is the active R-isomer of albuterol
- Levalbuterol is a short-acting beta-2 agonist used to treat bronchospasms
- Ensure proper administration of the inhaler or procedure for nebulization
- Levalbuterol is thought to have fewer adverse reactions compared with albuterol, but this has not been proven in clinical studies
- Levalbuterol is commonly used in children due to the belief that there are fewer adverse reactions associated with its use

Olodaterol

Brand Name

Striverdi Respimat

Generic Name

Olodaterol

Rx

Dosage Form

2.5 µg aerosol solution per actuation

Usage

Maintenance treatment of COPD

Pregnancy Category C

Dosing

Maximum of 2 inhalations once per day

Contraindications

Use as monotherapy in the treatment of asthma

Counseling Points

- Do not use for acute attacks
- Use proper administration technique:
  1. Shake the inhaler well immediately before each use. Then remove the cap from the mouthpiece.
  2. Prime the inhaler before using it for the first time and when the inhaler has not been used for >21 days. Prime by releasing four sprays into the air away from your face. If the inhaler has not been used for >3 days (but ≤ 21 days), prime once before use.
  3. When dose is ready to be administered, breathe in slowly through the mouth and press the dose release button; continue to breathe in slowly as long as possible, then hold breath for 10 seconds or for as long as is comfortable
  4. Repeat for second inhalation
  5. Breathe out deeply

Key Points

- **Black Box Warning:**
  - Asthma-related deaths: [U.S. Boxed Warning]: Long-acting beta-2 agonists (LABAs) increase the risk of asthma-related deaths
- Olodaterol is a long-acting beta-2 selective agonist
- Should only be used in combination with inhaled corticosteroids in asthma
- Should not be used for acute bronchospasm

◉ Salmeterol

Brand Name

Serevent Diskus

Generic Name

Salmeterol

Rx

Dosage Form

Powder for inhalation

Mechanism of Action

Salmeterol is a long-acting beta-2 agonist that produces bronchodilation by relaxing smooth muscles of the bronchioles

Usage

Chronic maintenance of asthma with inhaled steroid, maintenance treatment of COPD, prevention of exercise-induced bronchospasm

Pregnancy Category C

Dosing

- Age ≥ 4 years in asthma and COPD: 1 inhalation twice daily (morning and evening)
  - *Note:* Should only be used with an inhaled corticosteroid in the treatment of asthma
- Exercise-induced asthma: One inhalation 30 minutes before exercise

Adverse Reactions: Rare/Severe/Important

Anaphylaxis due to lactose component in oral inhalation powder may increase the risk of asthma-related deaths

Major Drug Interactions

Drugs Affecting Salmeterol

Strong inhibitors of CYP3A4: Affect salmeterol concentrations, increasing risk of cardiovascular effects

Contraindications

Use as monotherapy in asthma, treatment of acute asthma/COPD exacerbations, history of a severe allergic reaction to milk proteins (formulation contains lactose)

Counseling Points

- Do not use for acute attacks
- Use proper administration technique for Diskus:
  1. Activate the dry powder inhaler by sliding the activator. Every time the lever is pushed back, a dose is ready to be inhaled. Do not close or tilt the Diskus after the lever is pushed back.
  2. Breathe out deeply
  3. Inhale the powder contents completely
- Do not wash the Diskus. Keep it dry.
- Do not use more frequently than recommended dose

Key Points

- Salmeterol is a long-acting beta-2 selective agonist
- Should only be used in combination with inhaled corticosteroids in asthma
- Should not be used for acute bronchospasm
- Use caution with medications that are inhibitors of CYP3A4

COMBINATION COLD AND COUGH PRODUCTS

Introduction

Combination cold and cough products contain guaifenesin, which acts as an expectorant; or an antihistamine, which alleviates upper respiratory cold symptoms; and a narcotic or narcotic derivative as a cough suppressant. These agents should be used short term to treat symptoms of a cough and cold. The preparations containing narcotics are scheduled controlled substances and have abuse potential. The most common adverse effect of these agents is sedation. Cough and cold preparations are no longer recommended in children < 2 years of age due to the potential for dosing errors. There is no evidence that cough-suppressant therapy can prevent coughing. These drugs do not resolve the underlying pathophysiology that is responsible for the coughing. In patients with cough due to upper respiratory infection, cough suppressants have limited efficacy and are not recommended for this use. In patients with chronic bronchitis, cough suppressants, such as codeine and dextromethorphan are recommended for the short-term symptomatic relief of coughing. In patients with acute cough due to the common cold, OTC combination cold medications, with the exception of older antihistamine–decongestants, are not recommended due to the lack of supportive evidence. Expectorants have not been consistently shown to be effective either.

Members of the Drug Class

In this section: Guaifenesin and codeine, guaifenesin with dextromethorphan, hydrocodone and chlorpheniramine, promethazine with codeine

Others: Benzonatate (covered in an earlier section), carbetapentane

◉ Guaifenesin and Codeine

Brand Names

Robitussin AC, Guaiatussin AC, M-Clear (multiple)

Generic Name

Guaifenesin and codeine

Rx Only

Schedule V (capsules, liquid)

Dosage Form

Liquid

Mechanism of Action

Guaifenesin enhances the removal of mucus by decreasing its viscosity and surface tension. Codeine has a central mechanism of action on opioid receptors in the medullary cough center and may also have additional peripheral action on cough receptors in the proximal airways.

Usage

Temporary relief of cough and chest congestion

Pregnancy Category C

Some liquid preparations may contain alcohol and can be teratogenic if consumed in large quantities during pregnancy

Dosing

- Children:
  - 6 to 11 years:
    - Guaifenesin 100–200 mg and codeine 5–10 mg every 4 to 6 hours, as needed for cough
    - Maximum dose: Guaifenesin 1200 mg/day and codeine 60 mg/day
  - ≥ 12 years: See adult dosing
  - Warning: Safety of products containing codeine have been questioned in children < 18 years because of the potential to cause slowed or difficulty in breathing, especially in children who had tonsillectomy or had adenoids removed
- Adults:
  - Guaifenesin 200–400 mg and codeine 10–20 mg every 4 to 6 hours, as needed for cough
  - Maximum dose: Guaifenesin 2400 mg/day and codeine 120 mg/day

Adverse Reactions: Most Common

CNS depression, sedation, constipation, headache, respiratory depression, urinary retention, itching

Adverse Reactions: Rare/Severe/Important

Excessive sedation, respiratory depression (codeine), nephrolithiasis

Major Drug Interactions

Drugs Affecting Guaifenesin with Codeine

- CNS depressants: May enhance the effect and increase adverse reactions
- Benzodiazepines: May result in excess sedation, slowed/difficulty breathing or death
- CYP2D6 inhibitors: May decrease the effects of codeine by preventing the formation of its active metabolite

Counseling Points

- Avoid alcohol, which may increase the sedative effects
- Follow each dose with a full glass of water
- Sugar-free formulations are available

Key Points

- Schedule V controlled substance
- Use with caution in children < 18 years old as there may be an increased risk of adverse effects and difficulty breathing
- Using more than the recommended amount can cause CNS depressant effects and respiratory depression

- Should be administered under close supervision to individuals with a history of drug abuse or dependence
- Commonly used for cough

Guaifenesin with Dextromethorphan

Mechanism of Action

Guaifenesin enhances the removal of mucus by decreasing its viscosity and surface tension. Dextromethorphan is the D-isomer of the codeine analog methorphan and has no analgesic or addictive properties. Dextromethorphan depresses the cough center in the medulla.

Brand Names

Mucinex DM, Coricidin HBP Chest Congestion and Cough, Vicks 44E, Robitussin Peak Cold Cough + Chest Congestion DM (multiple brands available)

Generic Name

Guaifenesin with dextromethorphan

OTC

Dosage Forms

Liquid, tablet, capsule, extended-release tablet, granules

Usage

Temporary relief of cough and chest congestion

Pregnancy Category C

Some liquid preparations may contain alcohol and can be teratogenic if consumed in large quantities during pregnancy

Dosing

- Children 2 to 6 years:
  - Guaifenesin 50–100 mg and dextromethorphan 2.5–5 mg every 4 hours, as needed
  - Maximum dose: Guaifenesin 600 mg/day and dextromethorphan 30 mg/day
- Children 6 to 12 years:
  - Guaifenesin 100–200 mg and dextromethorphan 5–10 mg every 4 hours, as needed
  - Maximum dose: Guaifenesin 1200 mg/day and dextromethorphan 60 mg/day
- Children >12 years and Adults:
  - Guaifenesin 200–400 mg and dextromethorphan 10–20 mg every 4 to 6 hours as needed
  - Maximum dose: Guaifenesin 2400 mg and dextromethorphan 120 mg over 24 hours

Adverse Reactions: Most Common

Drowsiness, dizziness, headache, lightheadedness

Adverse Reactions: Rare/Severe/Important

Serotonin syndrome, confusion, excitement, irritability, nervousness

Major Drug Interactions

Drugs Affecting Guaifenesin with Dextromethorphan

- MAOIs and other serotonin modulators: May cause hypertension, hyperpyrexia, agitation, confusion, hallucinations (serotonin syndrome)
- 2D6 inhibitors such as paroxetine, fluoxetine, duloxetine, cinacalcet, amiodarone, bupropion, quinidine, terbinafine: may increase the risk of serotonin syndrome or CNS adverse effects (confusion, excitement, irritability, nervousness)

Contraindication

Use with or within 14 days of an MAOI

Counseling Points

- Follow each dose with a full glass of water
- Do not crush or chew extended-release preparations
- May cause sedation
- Do not take more than prescribed or indicated on product labeling

Key Points

- Multiple dosage forms and strengths available
- Available OTC
- May cause drowsiness and sedation
- Sugar-free formulations are available
- Assess for possible drug interactions

Hydrocodone and Chlorpheniramine

Mechanism of Action

Chlorpheniramine competitively antagonizes H1 receptors peripherally and centrally, blocking the increased capillary permeability (edema/wheel formation) and itching caused by histamine release and decreases rhinorrhea. Chlorpheniramine is less prone to cause drowsiness than other H1 receptor antagonists and may cause CNS stimulation. Hydrocodone is an opioid that depresses the cough center in the medulla.

Brand Names

Tussionex Pennkinetic ER, TussiCaps

Generic Name

Hydrocodone and chlorpheniramine

Rx Only

Schedule II controlled substance

Dosage Forms

Extended-release liquid, extended-release capsule

Usage

Temporary relief of cough associated with allergy or a cold

Pregnancy Category C

Dosing

- Children 6 to 11 years:
  - Half-strength capsule (5 mg hydrocodone/4 mg chlorpheniramine per capsule):
    - 1 capsule every 12 hours
    - Maximum dose: 2 capsules every 24 hours
  - Liquid (5 mg hydrocodone/4 mg chlorpheniramine per 2.5 ml):
    - 2.5 ml every 12 hours
    - Maximum dose: 5 ml every 24 hours
- Children ≥ 12 years and Adults:
  - Full-strength capsule (10 mg hydrocodone/8 mg chlorpheniramine):
    - 1 capsule every 12 hours
    - Maximum dose: 2 capsules every 24 hours
  - Liquid (10 mg hydrocodone/8 mg chlorpheniramine per 5 ml):
    - 5 ml every 12 hours
    - Maximum dose: 10 ml every 24 hours
- Renal and hepatic impairment: Use with caution in severe renal or hepatic impairment

Adverse Reactions: Most Common

Drowsiness, fatigue, constipation, dry mouth, headache, dizziness, nausea, vomiting, mood changes

Adverse Reactions: Rare/Severe/Important

Physical dependence (hydrocodone component), respiratory depression (hydrocodone component), urinary retention

Major Drug Interactions

Drugs Affecting Hydrocodone and Chlorpheniramine

- Alcohol and CNS depressants: Potentiate drowsiness; other anticholinergic drugs potentiate side effects
- Benzodiazepines: May result in excess sedation, slowed/difficulty breathing, or death
- CYP3A4 inhibitors may increase the concentration of hydrocodone

Contraindication

- Children < 6 years of age
- Caution in patients with urinary retention or narrow-angle glaucoma

Counseling Points

- Shake suspension well before using
- May cause drowsiness; Use caution when driving
- Take only as prescribed

Key Points

- **Black Box Warning:**
  - Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Avoid use of opioid cough medications in patients taking benzodiazepines, other CNS depressants, or alcohol.
- Schedule II controlled substance
- Should be administered under close supervision to individuals with a history of drug abuse or dependence

Promethazine with Codeine

Mechanism of Action

Promethazine reversibly, competitively antagonizes H1 receptors peripherally. Codeine depresses the cough center in the medulla.

Brand Name

Phenergan with Codeine

Generic Name

Promethazine with codeine

Rx Only

Schedule V controlled substance

Dosage Form

Liquid

Usage

Temporary relief of cough and upper respiratory symptoms due to allergy and common cold

Pregnancy Category C

Dosing

- Children:
  - 6 to 11 years:
    - 2.5–5 ml every 4 to 6 hours
    - Maximum dose: 30 ml every 24 hours
  - ≥ 12 years: See adult dosing
- Adults:
  - 5 ml every 4 to 6 hours
  - Maximum dose: 30 ml in 24 hours
- Renal dosage adjustment: Reduce dose in cases of renal impairment
- Hepatic dosage adjustment: Reduce dose in cases of hepatic impairment

Adverse Reactions: Most Common

Drowsiness, blurred vision, constipation, dry mouth, headache, fatigue, dizziness, nausea, photosensitivity (also see promethazine)

Adverse Reactions: Rare/Severe/Important

Physical dependence (codeine component), respiratory depression (codeine component) [also see promethazine]

Major Drug Interactions

Drugs Affecting Promethazine with Codeine

- Alcohol and CNS depressants: Potentiate drowsiness
- Other anticholinergic drugs: Potentiate side effects

Contraindications

- Children < 6 years of age
- Use in children for postoperative pain associated with a tonsillectomy or adenoidectomy
- In the treatment of respiratory symptoms associated with asthma

Counseling Points

- May cause drowsiness; exercise caution when driving
- Take with food to reduce GI upset
- Avoid prolonged exposure to sunlight
- Take only as prescribed

Key Points

- **Black Box Warnings:**
  - Promethazine/codeine is contraindicated in pediatric patients younger than 6 years due to the risk of respiratory depression. The risk is the highest when used with other respiratory depressants.
  - Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a cytochrome P450 (CYP-450) 2D6 polymorphism
  - Concomitant use of opioids with benzodiazepines, other CNS depressants or alcohol, may result in excess sedation, respiratory depression, coma, and death
- Schedule V controlled substance
- Should be administered under close supervision to individuals with a history of drug abuse or dependence
- Not recommended for use in patients with chronic respiratory disease

CORTICOSTEROIDS, INHALED

Introduction

Inhaled corticosteroids are used for the chronic treatment of asthma. These agents are also used in the chronic treatment of COPD and added to a long-acting bronchodilator in patients at a high risk of developing an exacerbation. Their exact mechanism of action is unknown, but they are thought to decrease inflammatory cells and cause smooth muscle relaxation. The lowest possible dose should be used to avoid adverse reactions. The most common adverse reactions include hoarseness, dry mouth, and oral candidiasis. Patients should be counseled on the proper use of the inhalation devices, to rinse their mouth after each use, and to use as directed. They should not be used as rescue inhalers.

Mechanism of Action for the Drug Class

Inhaled corticosteroids do not directly affect airway smooth muscle. Inhaled corticosteroids decrease the number of inflammatory cells (basophils, mast cells, neutrophils, eosinophils, macrophages, and lymphocytes) and inflammatory mediators (histamines, leukotrienes, cytokines), leading to decreased airway edema and hyper-responsiveness of smooth muscle. Steroids also inhibit mucus secretion in the airways.

Usage for the Drug Class

Chronic maintenance of asthma, COPD

Rx

Adverse Reactions for the Drug Class: Most Common

Hoarseness, pharyngitis, dry mouth, coughing, headache, oral candidiasis

Adverse Reactions for the Drug Class: Rare/Severe/Important

Adrenal insufficiency, growth suppression in children, cataracts, respiratory infection

Counseling Points for the Drug Class

- Rinse mouth with water after each use to prevent oral thrush
- It may take 1 to 4 weeks to see maximal benefit
- Use every day
- Do not use for acute attacks
- You must have a rescue inhaler available for breakthrough attacks
- Learn the proper administration technique for each inhalation device

Key Points for the Drug Class

- Used in the chronic treatment of asthma and to prevent frequent exacerbation in chronic COPD
- Should not be used for treatment of exacerbations
- It may take 1 to 4 weeks to see maximal benefit
- Rinse mouth after each use
- Fluticasone and budesonide should be avoided with CYP3A4 inhibitors, specifically protease inhibitors. Cushing's syndrome has been reported with concomitant use of these agents.

Members of the Drug Class

In this section: Beclomethasone, budesonide, fluticasone
Others: Ciclesonide, mometasone, flunisolide

◉ Beclomethasone

Brand Names

QVAR

Generic Name

Beclomethasone

RX

Dosage Forms

Inhalation aerosol

Pregnancy Category C

Dosing

- Children:
  - Five to 11 years:
    - Usual daily dose: 40 µg inhaled by mouth twice daily
    - Maximum dose: 80 µg inhaled by mouth twice daily
  - ≥ 12 years: See adult dosing
- Adults:
  - Previous therapy of bronchodilators only:
    - Initial dose: 40–80 µg twice daily
    - Maximum dose: 320 µg twice day
  - Previous therapy of inhaled corticosteroids:
    - Initial dose: 40–160 µg twice daily
    - Maximum dose: 320 µg twice daily

Major Drug Interactions

None

Counseling Points

- It is recommended to prime the QVAR inhaler before first use and when the inhaler has not been used for > 10 days. Prime by releasing 2 actuations into the air, away from your eyes and face.
- Use the dose counter on the inhaler to keep track of how many doses are left before the inhaler should be replaced

Equivalent Dosage Chart of Low, Medium, and High Doses Based On Age

	Low Dose (µg)			Medium Dose (µg)		High Dose (µg)	
Drug	**Age ≤ 5 years**	**Age 6–11 years**	**Adults**	**Age 6–11 years**	**Adults**	**Age 6–11 years**	**Adults**
Beclomethasone	100	50–100	100–200	< 200–400	200–400	> 200	> 400
Budesonide inhaler		100–200	200–400	> 200–400	> 400–800	> 400	> 800
Budesonide nebulizer	250–500	250–500		> 500–1000		> 1000	
Fluticasone furoate		N/A	100	N/A	n/a		200
Fluticasone propionate	100	100–200	100–250	> 200-400/500	> 250–500	> 400–500	> 500
Mometasone	N/A	110	110–220	≥ 220–<440	> 220–440	≥ 440	> 440
Triamcinolone	N/A	400–800	400–1000	> 800–1200	> 1000–2000	> 1200	> 2000

Budesonide

Brand Names
Pulmicort Flexhaler, Pulmicort Respules

Generic Name
Budesonide

Rx

Dosage Forms
Powder for oral inhalation, suspension for nebulization

Pregnancy Category B

Dosing
- Powder for oral inhalation (Flexhaler):
  - Children age ≥ 6 to years:
    - Initial dose: 180 µg twice daily (some patients may be initiated at 360 µg twice daily)
    - Maximum dose: 360 µg twice daily
  - Adults:
    - Initial dose: 360 µg twice daily (selected patients may be initiated at 180 µg twice daily)
    - Maximum dose: 720 µg twice daily
- Suspension for nebulization:
  - Children 12 months to 8 years:
    - Initial dose: 0.25 mg/day
    - Previous therapy of bronchodilators alone: 0.5 mg/day administered as a single dose or divided twice daily, up to a maximum daily dose of 0.5 mg
    - Previous therapy of inhaled corticosteroids: 0.5 mg/day administered as a single dose or divided twice daily, up to a maximum daily dose of 1 mg
    - Previous therapy of oral corticosteroids: 1 mg/day administered as a single dose or divided twice daily, up to a maximum daily dose of 1 mg

Contraindication
Severe hypersensitivity to milk proteins (Flexhaler)

Major Drug Interactions
Drugs Affecting Budesonide

Strong CYP3A4 inhibitors: May increase budesonide concentrations and increase systemic exposure

Counseling Points
- Ensure proper use of the Flexhaler:
  1. Prime the inhaler before first use (you do not have to prime the inhaler ever again). Take off the cover, hold the inhaler in the middle, and twist the brown grip one way all the way it will go and then twist in the opposite direction (you will hear a click). Repeat.
  2. Load the dose. Take off the cover, hold the inhaler in the middle, and twist the brown grip one way as far as it will go and then twist in the opposite direction (you will hear a click).
  3. Inhale the dose. Exhale away from the inhaler (do not blow into the mouthpiece), place the mouthpiece to the mouth, and seal your lips around the mouthpiece. Inhale as deeply as possible. When inhale is complete, place the cover back on the inhaler.
- Do not immerse the inhaler in water. Wipe outside of inhaler with a dry tissue once weekly.
- Use Pulmicort Respules only with a jet nebulizer; do not mix with other inhaled medications in the nebulizer

Fluticasone

Brand Names
Arnuity Ellipta, Flovent HFA, Flovent Diskus

Generic Name
Fluticasone propionate, fluticasone furoate

Rx

Dosage Forms
Breath activated aerosol powder (Arnuity Ellipta), metered-dose inhaler (MDI) HFA, powder for oral inhalation (Flovent Diskus)

Pregnancy Category
Adverse events were observed in animal studies but the overall risk of teratogenic effects was not increased. Women with poorly controlled asthma during pregnancy may lead to adverse outcomes of the fetus and asthma control should be monitored and optimized in pregnant women. Inhaled corticosteroids will prevent asthma exacerbations in pregnant women and it is recommended that therapy should be continued throughout pregnancy.

Dosing
- Fluticasone furoate:
  - Children > 12 years and Adults:
  - No prior treatment with inhaled corticosteroids: 100 µg daily (Maximum: 200 µg/day)
  - Prior treatment with inhaled corticosteroids: 100–200 µg daily (Maximum: 200 µg/day)
- HFA/MDI:
  - Children:
    - 4 to 11 years:
      - Initial dose: 88 µg inhaled twice daily
      - Maximum dose: 88 µg inhaled twice daily
  - Children > 12 years of age and adults:
    - Previous therapy of bronchodilator alone:
      - Initial dose: 88 µg twice daily
      - Maximum dose: 440 µg twice daily
    - Previous therapy of inhaled corticosteroids:
      - Initial dose: 88–220 µg twice daily
      - Maximum dose: 440 µg twice daily

- Previous therapy of oral corticosteroids (OCS):
  - Initial dose: 440 µg twice daily
  - Maximum dose: 880 µg twice daily
- Diskus, dry powder inhaler:
  - Children:
    - 4 to 11 years:
      - Initial dose: 50 µg twice daily, up to a maximum of 100 µg twice daily
  - Children >12 years of age and adults:
    - Previous therapy of bronchodilator only:
      - Initial dose: 100 µg twice daily
      - Maximum dose: 500 µg twice daily
    - Previous therapy of inhaled corticosteroids:
      - Initial dose: 100–250 µg twice daily
      - Maximum dose: 500 µg twice daily
    - Previous therapy of oral corticosteroids:
      - Initial dose: 500–1,000 µg twice daily
      - Maximum dose: 1,000 µg twice daily

Major Drug Interactions

Drugs Affecting Fluticasone

Strong CYP3A4 inhibitors: Increased systemic concentrations of fluticasone have been found with the concomitant use of these agents, leading to increased systemic adverse effects. Use is not recommended.

Counseling Points

- Breath activated powder, fluticasone furoate, Arnuity Ellipta: Remove the inhaler from the foil tray. The inhaler contains 30 doses, as indicated on the dose counter. Do not open the cover until you are ready to inhale a dose. Do not close the cover until after you have inhaled the medicine. Slide the cover down to expose the mouthpiece and you should hear a click. While holding the inhaler away from you, breathe out fully. Do not breathe into the mouthpiece. Place the mouthpiece between your lips and close your lips firmly around it. Take a long, steady breath through your mouth. Do not breathe through your nose. Remove the inhaler from your mouth and hold your breath for 3 to 4 seconds. Breathe out slowly and gently. Close the cover over the mouthpiece. Rinse your mouth with water after you use the inhaler and spit the water out. Do not wash the inhaler or place in water.
- Aerosol inhalation: Flovent HFA must be primed before first use, when not used for 7 days or more or if dropped. To prime the first time, release 4 sprays into the air. Shake well before each spray and spray away from face. If dropped or not used for 7 days or more, prime by releasing a single test spray. See the albuterol HFA for instructions on use.
- Flovent Diskus: Do not use with a spacer device. Do not exhale into the Diskus. Do not wash or take apart. Use in horizontal position. Take a deep quick breath. See Fluticasone/Salmeterol Diskus for instructions on use.

Key Points

- Instruct on proper use of inhalation device
- Dosage varies based on inhalation device
- Commonly used with asthma or COPD
- Monitor for drug interactions with CYP3A4 inhibitors. Drug therapy may need to be adjusted in patients with some drug interactions.

CORTICOSTEROIDS, INTRANASAL

Introduction

Intranasal corticosteroids are primarily used for rhinitis and occasionally for the prevention of nasal polyps. They are also used as an adjunct in the treatment of rhinosinusitis. The maximal benefit of these agents may not be seen for 1 to 2 weeks. The most common adverse reactions include epistaxis and nasal irritation. All patients should be counseled on the proper administration technique of intranasal products and instructed to blow their nose before use.

Mechanism of Action for the Drug Class

Corticosteroids may decrease the number of inflammatory mediators. They may also reverse dilatation and increase vessel permeability in the area, resulting in decreased entry of cells to the sites of damage to reduce or control inflammation.

Usage for the Drug Class

Relief of symptoms of seasonal and perennial allergic rhinitis, nonallergic rhinitis, prevention of nasal polyps, adjunct in the treatment of rhinosinusitis

Adverse Reactions for the Drug Class: Most Common

Headache, dizziness, epistaxis, throat discomfort, nasal irritation

Adverse Reactions for the Drug Class: Rare/Severe/Important

Nasal ulcerations, nasal candida infections, nasal septum perforations, glaucoma/cataracts

Major Drug Interactions for the Drug Class

None

Counseling Points for the Drug Class

- Blow your nose before each use
- Insert the applicator into the nostril. Keeping the bottle upright, tilt your head forward slightly and close of the other nostril. Breathe in through the nose. While inhaling, press pump to release spray. Do not spray directly onto the wall between the two nostrils (the septum).
- Avoid blowing your nose for 10 to 15 minutes after use
- Intranasal corticosteroids do not provide immediate relief of nasal symptoms
- If symptoms are not relieved after 1 to 3 weeks, discontinue use and contact physician.
- If taking two sprays and symptoms are adequately controlled, can reduce to one spray in each nostril.

Key Points for the Drug Class

- Most commonly used for seasonal and allergic rhinitis
- Do not provide immediate relief of symptoms
- Administer by nasal inhalation only
- Caution not to spray into eyes

Members of the Drug Class

In this section: Beclomethasone, budesonide, fluticasone, mometasone, triamcinolone
Others: Ciclesonide, flunisolide

◉ Beclomethasone

Brand Names

Beconase AQ, Qnasl, Qnasl Children's

Generic Name

Beclomethasone

Rx

Dosage Form

Nasal inhalation

Pregnancy Category C

Dosing

- Children:
  - Children 6 to 11 years of age:
    - Beconase AQ: 1 spray (42 µg) into each nostril twice daily
    - Maximum dose: Eight sprays every 24 hours
  - Children >12 years of age and adults:
    - Beconase AQ:
      - Initial dose: One to two sprays (42-84 µg) into each nostril twice daily
      - Maximum dose: Eight sprays every 24 hours
    - Qnasl Children's
      - Four to 11 years of age: 1 inhalation (40 µg) in each nostril daily (Maximum: 80 µg daily)
    - Qnasl: Children >12 years of age and adults:
    - Initial dose: 2 sprays (160 µg) in each nostril once daily
    - Maximum dose: 4 sprays every 24 hours

Counseling Points

- Beconase AQ: Shake well prior to each use. Prior to initial use, prime pump 6 times (or until fine spray appears); repeat priming if product not used for ≥ 7 days. Nasal applicator and dust cap may be washed in warm water and dried thoroughly.
- Qnasl: Shake well prior to each use. Prior to initial use, prime pump 4 times. If product not used for ≥ 7 days, prime pump 2 times.
- Spray in nostril(s); avoid spraying in eyes or mouth

◉ Budesonide

Brand Name

Rhinocort Allergy

Generic Name

Budesonide

OTC

Dosage Form

Nasal inhalation

Pregnancy Category B

Dosing

- Children 6 to 12 years of age: 1 spray (32 µg) into each nostril once daily
  - Maximum 2 sprays (64 µg) in each nostril once daily
- Children > 12 years of age and adults: 2 sprays (64 µg) in each nostril once daily every 24 hours

Major Drug Interactions

Drugs Affecting Budesonide

Strong inhibitors of CYP3A4: May increase serum concentration

Counseling Points

- Shake the inhaler before each use
- Nasal inhaler must be primed before first use and if not used for more than 2 days in a row. To prime the inhaler before first use, remove the cap, shake gently, and press down on the white collar 8 times. If not used for more than 2 days in a row, prime the inhaler with 1 spray or until a fine mist appears.

Fluticasone

Brand Names

Flonase Allergy Relief, Flonase Sensimist

Generic Name

Fluticasone furoate, fluticasone propionate

OTC

Dosage Forms

Nasal inhalation, intranasal suspension

Pregnancy Category C

Dosing

- Flonase (fluticasone propionate) and Flonase Sensimist (fluticasone furoate):
  - Children 4 to 11 years of age:
    - Usual dose: 1 spray into each nostril once daily
  - Children ≥ 12 and a adults:
    - Usual dose: 2 sprays into each nostril once daily

Major Drug Interactions

Drugs Affecting Fluticasone

Strong CYP3A4 inhibitors: Increased systemic concentrations of fluticasone have been found with the concomitant use of these agents, leading to increased systemic adverse effects. Use is not recommended.

Counseling Points

- Shake contents before each use
- Prime pump prior to first use or if spray is unused for ≥ 7 days.
- Flonase: Remove the cap from the bottle. Blow your nose gently to clear nostrils. Insert the applicator into the nose, aiming slightly away from the center of your nose and close the other nostril. Breathe in gently through your nose. While inhaling, press pump to release spray once or twice. Breathe out through your mouth. Repeat in other nostril.
- Do not spray into eyes

Mometasone

Brand Name

Nasonex

Generic Name

Mometasone

Rx

Dosage Form

Nasal inhalation

Pregnancy Category C

Dosing

- Children 2 to 11 years of age: Usual dose is one spray into each nostril daily
- Children ≥ 12 years of age and adults: Usual dose is two sprays into each nostril once daily

Counseling Point

- Before you use Nasonex for the first time, prime the pump by pressing downward on the shoulders of the white nasal applicator 10 times or until a fine spray appears. If unused for more than 1 week, reprime by spraying 2 times or until a fine spray appears. Shake before using. Remove the cap from the bottle. Blow your nose gently to clear nostrils. Insert the applicator into the nose, aiming slightly away from the center of your nose and close the other nostril. Breathe in gently through your nose. While inhaling, press pump to release spray once or twice. Breathe out through your mouth. Repeat in other nostril.
- Do not spray into eyes

Triamcinolone

Brand Name

Nasacort Allergy 24HR, Nasacort Allergy 24H Children

Generic Name

Triamcinolone

OTC

Dosage Form

Nasal inhalation

Pregnancy Category C

Dosing

- Children 2 to 5 years of age:
  - Usual dose: One spray into each nostril once daily

- Children 6 to 11 years of age:
  - Usual dose: 1 spray into each nostril once daily
  - Maximum dose: 4 sprays every 24 hours
- Children ≥12 years of age and adults:
  - Usual dose: 2 sprays into each nostril once daily
  - Maximum dose: 4 sprays every 24 hours

Counseling Point

Prime prior to first use, discharging 5 sprays into the air. If product is not used for more than 2 weeks, reprime with one spray.

DECONGESTANTS

Introduction

Decongestants are used for temporary relief of nasal congestion due to a cold or rhinitis. There are topical and systemic decongestants available over-the-counter. Oxymetazoline is a topical decongestant that should not be used >3 days due to the risk of rebound congestion. Patients with coronary heart disease and hypertension should use these agents with caution and in severe cases, the use in these patients is contraindicated. The most common adverse effects for topical agents include restlessness, nasal dryness, and sneezing. The most common adverse effects associated with pseudoephedrine use include irritability, insomnia, nausea, dizziness, palpitations, and dry mouth. Pseudoephedrine is available in combination with antihistamines, cough suppressant and expectorants. Pseudoephedrine has been abused and used to make methamphetamine. Due to the misuse of pseudoephedrine, the quantity of purchase is limited and must be requested from the pharmacy counter.

Members of the Drug Class

In this section: Oxymetazoline, pseudoephedrine
Others: Naphazoline, phenylephrine, tetrahydrozoline, phenylephrine

◉ Oxymetazoline

Mechanism of Action

Stimulate alpha-adrenergic receptors of vascular smooth muscle, resulting in relief of nasal congestion. Intranasal administration results in constriction of dilated blood vessels in the nasal mucosa, reducing blood flow to engorged edematous tissue. These effects promote drainage of the sinuses, relieving nasal stuffiness, and improving nasal ventilation

Brand Names

Afrin, Dristan, Mucinex Nasal Spray, Vicks Sinex

Generic Name

Oxymetazoline

OTC

Dosage Form

Intranasal solution

Usage

Temporary relief of nasal congestion due to the common cold, sinusitis, and allergies; adjunctive therapy for middle ear infections associated with acute or chronic rhinitis

Pregnancy Category

Adverse fetal effects have not been observed following maternal doses during the third trimester but have not been formally studied. Adverse effects have been noted when large doses have been used or when used for a longer-than-recommended duration.

Dosing

- Adults and children ≥ 6 years of age, 0.05% solution:
  - Usual dose: 2 to 3 sprays in each nostril up to twice daily for ≤ 3 days
  - Maximum dose: 2 doses every 24 hours

Adverse Reactions: Most Common

Nasal dryness, nasal irritation/stinging, nasal congestion, insomnia, nausea, sneezing

Adverse Reactions: Rare/Severe/Important

Rebound congestion, high blood pressure, palpitations

Major Drug Interactions

Drugs Affecting Oxymetazoline

Tricyclic antidepressants, MAOIs: Potentiate the hypertensive effects of oxymetazoline but risk probably low with nasal preparations

Counseling Points

- For intranasal use only
- Wipe the tip of the applicator clean after each use
- Do not share the container with another individual
- Prior to initial use of sprays, the nasal inhalers should be primed by pressing the pump several times
- Sprays should be pumped into each nostril with the head erect so that excess solution is not released
- Insert nozzle into nostril, press rim and sniff/inhale through nostril deeply. Can repeat in other nostril. Wipe nozzle clean after each use.
- Do not use medication >3 days without your healthcare provider's recommendation due to potential occurrence of rebound congestion

Key Points

- Used for the temporary relief of nasal congestion
- Do not use more than recommended dose
- Use with caution in patients with coronary heart disease, angina, hypertension, enlarged prostate, glaucoma, and hyperthyroidism
- Do not use >3 days unless prescribed by a healthcare provider due to risk of rebound congestion

◉ Pseudoephedrine

Mechanism of Action

Directly stimulates alpha-adrenergic receptors in the respiratory mucosa, causing vasoconstriction, which reduces the edema in the nasal mucous membranes and decreases edema and nasal and sinus congestion. It also acts, to a lesser degree, on the beta-adrenergic receptors, which may be responsible for some adverse cardiovascular effects.

Brand Names

Sudafed, Zephrex-D, Nexaphed, Children's Silfedrine, Shopko Nasal Decongestant (many)

Generic Name

Pseudoephedrine

OTC

OTC but need to be requested from the pharmacist at pharmacy counter and purchased quantities are limited

Dosage Forms

Tablets, extended-release tablets, oral liquid

Usage

Temporary relief of nasal congestion and pressure due to the common cold, upper respiratory allergy symptoms, and drainage of sinuses

Pregnancy Category

Based on limited human data, use during the first trimester is associated with a risk of gastroschisis, small intestine atresia, and hemifacial macrosomia and is not recommended. A single dose during the third trimester was not associated with any adverse effects but extended-release preparations used for multiple days are associated with fetal tachycardia

Dosing

- Immediate release:
  - Children:
    - Do not use in children < 2 years of age
    - 4 to 5 years: 15 mg PO every 4 to 6 hours (maximum dose: 60 mg/day)
    - 6 to 12 years: 30 mg PO every 4 to 6 hours (maximum dose: 120 mg/day)
  - Adults:
    - 60 mg PO every 4 to 6 hours (maximum 240 mg/day)
- Extended-release
  - Adults:
    - 120 mg every 12 hours or 240 mg every 24 hours
    - Do not crush or chew extended-release tablets

Adverse effects: Most common

Palpitations, tremors, dizziness, restlessness, dry mouth, nausea

Adverse Effects: Rare/Severe/ Important

Hypertension, insomnia, tachycardia, arrhythmias, seizures, anorexia, hallucinations, chest pain, blurry vision, urinary retention, kidney stones, anaphylaxis

Major Drug Interactions

Drugs Affecting Pseudoephedrine

- Monoamine oxidase inhibitors (MAO-I): May cause malignant hypertension and should be avoided
- Linezolid/tedizolid: May cause enhanced hypertensive effects; if used together, should be monitored carefully
- Ergot derivatives: May cause enhanced hypertensive effects and should be avoided

Pseudoephedrine's Effect on Other Drugs

- Sympathomimetics: May cause enhanced adverse effects
- Serotonin-norepinephrine reuptake inhibitors (duloxetine, venlafaxine, desvenlafaxine): May cause enhanced hypertensive and tachycardic effects

Contraindications

- With or within 14 days of using a monoamine oxidase inhibitor
- Use in patients with uncontrolled hypertension, significant coronary artery disease, and narrow-angle glaucoma or with urinary retention

Counseling Points

- Use with caution or with knowledge of a physician in patients with cardiovascular disease, controlled hypertension, glaucoma, seizure disorder, diabetes, or uncontrolled thyroid dysfunction
- Use is not recommended for more than 7 days or with a fever
- Do not crush extended-release tablets
- Do not use with other stimulant medications

Key Points

- The most common use is in the treatment of nasal congestion
- Available in combination with antihistamines and cough suppressants
- Use with caution in elderly: Use lowest possible dose, if necessary
- Not recommended in children < 2 years of age due to the potential for life-threatening adverse effects
- It is contraindication with use or within 14 days of a monoamine oxidase inhibitor and in patients with uncontrolled hypertension, severe coronary artery disease, glaucoma, and urinary retention.

EPINEPHRINE FOR ANAPHYLAXIS

Introduction

Epinephrine is an adrenergic agonist that stimulates alpha-1, beta-1 and beta-2 receptors, which constrict blood vessels to increase blood pressure, relax smooth muscles in the lungs to reduce wheezing and improve breathing, stimulates the heart (increases heart rate), and reduces hives and swelling that occur around the face and lips. It is considered the first-line medication of choice in anaphylaxis in an outpatient setting. Epinephrine is available in an auto-injector form for the treatment of an anaphylactic emergency.

◉ Epinephrine

Mechanism of Action

Epinephrine is a sympathomimetic catecholamine with numerous uses, based on various mechanisms of action. Epinephrine is a very potent activator of alpha-receptors, resulting in vasoconstriction and decreased vascular permeability. It also stimulates beta-1 and beta-2 receptors, resulting in relaxation of bronchial smooth muscle and stimulation of heart rate and cardiac contractility.

Brand Name

Adrenalin, Adrenaclick, EpiPen, EpiPen Jr, Auvi-Q

Generic Name

Epinephrine

Rx

Dosage Forms

Injection (vials, prefilled syringe, and auto-injectors)

Usage

Anaphylactic reactions, advanced cardiovascular life support (*ACLS*; ventricular fibrillation/pulseless ventricular tachycardia, pulseless electric activity, asystole), bradycardia, bronchospasms/asthma/wheezing, shock/hypotension

Pregnancy Category C

Dosing

- Anaphylaxis:
  - Pediatric dosing Auto-Injector:
    - Adrenaclick: IM, SubQ:
      - Children 15 to 29 kg: 0.15 mg; if anaphylactic symptoms persist, dose may be repeated using an additional Adrenaclick injector
      - Children ≥ 30 kg: 0.3 mg; if anaphylactic symptoms persist, dose may be repeated using an additional Adrenaclick injector
    - Auvi-Q: IM, SubQ:
      - Children 15 to 29 kg: 0.15 mg; if anaphylactic symptoms persist, dose may be repeated
      - Children ≥ 30 kg: 0.3 mg; if anaphylactic symptoms persist, dose may be repeated
    - EpiPen Jr: IM, SubQ:
      - Children 15 to 29 kg: 0.15 mg; if anaphylactic symptoms persist, dose may be repeated using an additional EpiPen Jr
    - EpiPen: IM, SubQ:
      - Children ≥ 30 kg: 0.3 mg; if anaphylactic symptoms persist, dose may be repeated using an additional EpiPen
  - Adult dosing:
    - IM (preferred)/SubQ: 0.2–0.5 mg every 5 to 15 minutes in the absence of clinical improvement
    - IV: 0.1 mg slow bolus (further diluted in 10 ml of normal saline) administered over 5 to 10 minutes
    - IM preferred)/SubQ (auto-injector): 0.3 mg; if symptoms persist, may repeat dose
    - Adrenaclick: IM, SubQ: 0.3 mg; if anaphylactic symptoms persist, dose may be repeated using an additional Adrenaclick injector
    - Auvi-Q: IM, SubQ: 0.3 mg; if anaphylactic symptoms persist, dose may be repeated
    - EpiPen: IM, SubQ: 0.3 mg; if anaphylactic symptoms persist, dose may be repeated using an additional EpiPen

Adverse Reactions: Most Common

Increased heart rate/tachyarrhythmia, headache, hyperglycemia, tremor, sweating

Adverse Reactions: Rare/Severe/Important

Ventricular arrhythmias, limb necrosis (with higher rates of infusion), worsening coronary artery disease or cerebrovascular disease

Major Drug Interactions

Drugs Affecting Epinephrine

- Beta blockers: Decrease efficacy of epinephrine's anti-anaphylactic effects; enhance vasopressor effects of epinephrine
- Vasodilators: Decrease efficacy

Contraindications

There are no absolute contraindications to the use of injectable epinephrine in a life-threatening situation

Counseling Points

- Auto-Injectors should be administered IM into the anterolateral aspect of the middle third of the thigh and can be administered through clothing, if necessary.
- A second dose should always be available and can be administered if response to first dose is inadequate. If anaphylactic symptoms persist after first dose, may repeat dose in 5 to 15 minutes; more than two sequential doses should only be administered under direct medical supervision
- Use proper administration technique via the EpiPen and EpiPen Jr Auto-Injector:
  1. Remove the EpiPen or EpiPen Jr auto-injector from the clear carrier tube
  2. Flip open the cap of the auto-injector
  3. Tip and slide the auto-injector out of the carrier tube
  4. Grasp the auto-injector in your fist with the needle end pointing downward
  5. With your other hand, remove the safety release by pulling straight up without bending or twisting it
  6. Place the needle end against the middle of the outer thigh (upper leg) at a right angle (perpendicular) to the thigh. Hold leg firmly.
  7. Swing and push the auto-injector firmly until it "clicks." The click signals that the injection has started.
  8. Hold firmly in place for 3 seconds
  9. Remove the auto-injector from the thigh
  10. Massage the injection area for 10 seconds
  11. Seek emergency medical help immediately
- Use proper administration technique via the Auvi Q:
  1. Pull Auvi-Q from the outer case
  2. Pull off safety guard (red in color)
  3. Place the black end of Auvi-Q against the middle of the outer thigh. Can be administered through clothing, if needed.
  4. Inject and hold in place for 5 seconds. Hold leg firmly.
  5. Replace the outer case
  6. Seek emergency medical help immediately

Key Points

- Epinephrine is used for a variety of acute indications, often in situations requiring immediate treatment. Its actions on alpha- and beta-receptors result in effective treatment of anaphylaxis, wheezing, and arrhythmias/circulatory shock.
- Auto-Injectors contain a single, fixed-dose of epinephrine
- IM administration in the anterolateral aspect of the middle third of the thigh is preferred, in the setting of anaphylaxis, as SubQ administration results in slower absorption and is less reliable than IM administration
- If anaphylactic symptoms persist after first dose, may repeat dose in 5 to 15 minutes; more than two sequential doses should only be administered under direct medical supervision
- Administer through clothing, if necessary
- Do not administer repeated injections at the same site. Do not inject into the buttocks or into digits, hands, or feet.
- Immediately seek medical help after administration of auto-injector

EXPECTORANTS

Introduction

Expectorants are used to thin respiratory secretions to make a cough more productive. These agents should be used for short-term treatment of a cough. If a cough persists >1 week, patients should be referred to a physician. Effectiveness is controversial. Guaifenesin is commonly found in combination with decongestants and antihistamines. Adverse effects are rare with guaifenesin.

Mechanism of Action for the Drug Class

Enhances the removal of viscous mucus by reducing mucin release, which decreases adhesiveness and surface tension of the mucus and increases mucociliary transport

Members of the Drug Class

In this section: Guaifenesin
Others: None

◉ Guaifenesin

Brand Names
Mucinex Chest Congestion, Mucinex, Tussin

Generic Name
Guaifenesin

OTC

Dosage Forms
Tablet, extended-release tablet, syrup, granules

Usage
Cough to help loosen phlegm

Pregnancy Category
Increased risk of adverse birth outcomes have not been observed in the limited studies available. Alcohol may be present in some syrup formulations which should not be consumed in pregnant women

Dosing
- Tablet, syrup:
  - Children:
    - 2 to 6 years:
      - Usual dose: 50–100 mg every 4 hours
      - Maximum dose: 600 mg every 24 hours
    - 6 to 11 years:
      - Usual dose: 100–200 mg every 4 hours
      - Maximum dose: 1200 mg every 24 hours
  - Children ≥ 12 years of age and adults:
    - Usual dose: 200–400 mg every 4 hours
    - Maximum dose: 2400 mg every 24 hours
- Extended-release tablets: Children ≥ 12 years of age and adults:
  - Usual dose: 600–1200 mg twice daily
  - Maximum dose: 2400 mg every 24 hours

Adverse Reactions: Most Common
Diarrhea, drowsiness, dizziness, headache

Adverse Reactions: Rare/Severe/Important
Nephrolithiasis with large doses, hypouricemia

Major Drug Interactions
None

Counseling Points
- Use caution with children < 2 years of age
- Follow each dose with a full glass of water
- Do not chew or crush or break extended-release formulations
- Sugar-free formulations are available

Key Points
- Used in the symptomatic treatment of cough associated with phlegm
- Supporting data are very limited and effectiveness is controversial.
- Guaifenesin is usually used in combination with decongestants, antihistamines, and antitussives
- Use cautiously in children. Ensure that doses are correct to avoid an overdose.

LEUKOTRIENE INHIBITOR

Introduction
Leukotriene inhibitors are primarily used in adults and children with chronic asthma. They are administered orally, which improves patient compliance with asthma therapy. These agents are not the preferred first-line treatment for persistent asthma. Montelukast is also used for allergic rhinitis and the prevention of exercise-induced bronchoconstriction. Granules are the preferred dosage form in children < 2 years of age. Chewable tablets or granules can be used for children > 2 years of age. Montelukast may interact with drug therapies affecting the CYP2C9 and CYP3A4 enzyme systems. Adverse reactions are minor and include headache, nausea, and diarrhea. Serious reactions that have been reported include elevated liver enzymes, eosinophilia, and neuropsychiatric symptoms.

Mechanism of Action for the Drug Class
Leukotrienes are produced by arachidonic metabolism and are released by various cells, including eosinophils and mast cells. Leukotriene receptors are found in the airways, where they can cause airway edema and constriction, and on pro-inflammatory cells. Leukotriene inhibitors selectively block leukotriene receptors in airways, thereby decreasing airway edema, relaxing smooth muscles, and inhibiting inflammatory responses. They also block leukotrienes produced in nasal mucosa following allergen exposure.

Members of the Drug Class
In this section: Montelukast
Others: Zafirlukast

◉ Montelukast

Brand Name
Singulair

Generic Name
Montelukast

Rx

Dosage Forms
Tablet, chewable tablet, oral granules

Usage
Prophylaxis and chronic treatment of asthma, second-line prevention of exercise-induced bronchoconstriction

Pregnancy Category B

Dosing
- Asthma or allergic rhinitis:
  - Children:
    - 12 months to 5 years of age: 4 mg by mouth once daily in the evening
    - 6 to 14 years of age: 5 mg by mouth once daily in the evening
- Exercise-induced bronchoconstriction:
  - 6 to 14 years of age: 5 mg by mouth once at least 2 hours prior to exercise
  - Children ≥15 years of age and adults: 10 mg by mouth once daily in the evening
- Exercise-induced bronchoconstriction: 10 mg by mouth at least 2 hours before exercise. Additional doses should not be taken in the same 24-hour period.

Adverse Reactions: Most Common
Headache, cough, pharyngitis, nausea, diarrhea, upper respiratory infection, fever, dermatitis

Adverse Reactions: Rare/Severe/Important
Churg-Strauss syndrome (eosinophilic vasculitis), neuropsychiatric symptoms (agitation, aggression, hallucinations, suicidal behavior), increased LFTs

Major Drug Interactions
Drugs Affecting Montelukast
- CYP3A4 inducers (phenobarbital and rifampin): Decrease concentration by 40%
- Gemfibrozil: May increase the serum concentration of montelukast

Counseling Points
- Not for acute attacks
- For control of asthma and allergic rhinitis, use every day
- Granules may be mixed with applesauce, formula, breast milk, or ice cream. Opened packets should be used within 15 minutes.
- When used for exercise-induced bronchoconstriction, take at least 2 hours before exercise
- Chewable tablets contain phenylalanine

Key Points
- Most commonly used as adjunct treatment for asthma or for allergic rhinitis
- Do not use for the treatment of acute symptomatic control of asthma
- Montelukast should not be used in patients with severe liver disease (has not been studied)
- Monitor patients for neuropsychiatric symptoms

XANTHINE DERIVATIVE

Introduction
Theophylline has been used for the treatment of asthma and COPD for decades. Currently, the role of theophylline is limited for these indications due to the introduction of inhaled bronchodilators and the potential for serious adverse reactions with xanthine derivatives. Theophylline is now considered last-line or adjunct therapy for these indications. Theophylline has a narrow therapeutic range, and changes in dosing should only occur after a serum concentration is obtained. Theophylline is metabolized by CYP1A2, CYP2E1, and CYP3A4 isoenzymes. Because of this, it may potentially interact with multiple medications. The most common adverse reactions are nausea and gastroesophageal reflux symptoms.

Mechanism of Action for the Drug Class
Theophylline is a nonselective phosphodiesterase (PDE) inhibitor. PDE inhibition and the concomitant elevation of cellular cAMP and cyclic guanosine monophosphate (cGMP) account for the bronchodilator action of theophylline. Several PDE isoenzymes have now been recognized; those important in smooth muscle relaxation include PDE3, PDE4, and PDE5. Theophylline is a weak inhibitor of all PDE isoenzymes. Theophylline may also have

anti-inflammatory effects in asthma by inhibiting infiltration of eosinophils and $CD4^+$ lymphocytes into the airways after allergen exposure. May stimulate the medullary respiratory center and promote catecholamine release.

Members of the Drug Class

In this section: Theophylline

◉ Theophylline

Brand Names

Theo-24, Elixophyllin-Kl, Theochron

Generic Name

Theophylline

Rx

Dosage Forms

Extended-release tablet, extended-release capsule, oral solution, injection

Usage

Symptomatic treatment or prevention of asthma, COPD, apnea in infants

Pregnancy Category C

Dosing

Dosing must be individualized based on age, weight, smoking history, evidence of heart failure, and liver function. Loading doses may be given to obtain therapeutic concentrations quickly but are usually not needed for maintenance therapy. Intravenous therapy used infrequently or not recommended for the treatment of acute symptoms.

Oral dosage forms:

- Children ≥ 1 year of age and < 45 kg:
  - Initial dose: 10–14 mg/kg/day divided every 4 to 6 hours (oral liquid)
  - Maximum initial starting dose: 300 mg/day
- Adults without risk factors for impaired theophylline clearance: Initial maintenance dose of 300–400 mg per day
- Hepatic dosage adjustment: Decrease dose by at least 50% in severe liver disease/cirrhosis and frequent monitoring is needed

Pharmacokinetic Monitoring

Therapeutic level 5–10 μg/ml for most indications. May increase to 15 μg/ml but there is limited benefit and may potentially see increased adverse reactions.

Adverse Reactions: Most Common

Gastroesophageal reflux, nausea, vomiting, headache, insomnia, nervousness, tremor

Adverse Reactions: Rare/Severe/Important

Seizures, cardiac arrhythmias, tachycardia, increased urination, or difficulty urinating

Major Drug Interactions

Drugs Affecting Theophylline

- Carbamazepine, phenytoin, phenobarbital, rifampin, ketoconazole, cigarette smoking, marijuana smoking, St. John's wort: Decrease serum concentrations
- Allopurinol, cimetidine, clarithromycin, ciprofloxacin, erythromycin, febuxostat, thyroid hormones, verapamil, zafirlukast, zileuton: Increase serum concentration

Theophylline's Effect on Other Drugs

- Lithium: Decreases levels

Contraindications

None

Essential Monitoring Parameters

Therapeutic blood concentration should be 5–15 μg/ml, with a target concentration of 5–10 μg/ml Serum theophylline concentrations should be monitored prior to making dose changes, in the presence of signs or symptoms of toxicity, when changing medications, or in the event of illness. Age, smoking status, liver function, and evidence of heart failure can alter theophylline clearance; doses may need to be adjusted in these patients.

Counseling Points

- Do not break, chew, or crush extended-release formulations
- Capsules may be sprinkled on small amount of food and swallowed whole without chewing
- Avoid smoking. Smoking can change the metabolism of theophylline.
- Avoid dietary stimulants (coffee, tea, chocolate) that may increase adverse effects

Key Points

- Theophylline should only be used as an adjunctive treatment in COPD and asthma
- Dosing must be individualized based on age, organ function, smoking history, and concomitant drug therapy
- Dose adjustment should not be made without drug concentration monitoring
- Most patients achieve a therapeutic effect with low likelihood of adverse effects at concentrations of 5–10 μg/ml
- Theophylline interacts with drugs that inhibit or induce CYP2E1, CYP1A2, or CYP3A4

MISCELLANEOUS RESPIRATORY AGENT

Introduction

Omalizumab is a recombinant DNA-derived monoclonal antibody that selectively binds to human immunoglobulin E (IgE) on mast cells and basophils and limits the release of mediators of the allergic response. Omalizumab is used for persistent moderate-to-severe allergic asthma not controlled on corticosteroids. Omalizumab has been shown to decrease asthma exacerbations in these patients. It should be administered subcutaneously by a healthcare professional in a healthcare setting in order to monitor for anaphylaxis. The package labeling for omalizumab contains a Black Box Warning for anaphylaxis and angioedema. A medication guide must be distributed to the patient before initiation of treatment.

Mechanism of Action for the Drug Class

Omalizumab is an IgG monoclonal antibody, which inhibits the binding of IgE to the high-affinity IgE receptor on the surface of mast cells and basophils. Reduction in surface—bound on IgE on the receptor limits the release of mediators of the allergic response and will decrease IgE levels. Treatment with omalizumab also reduces the number of receptors on basophils in atopic patients.

Members of the Drug Class

In this section: Omalizumab
Others: None

◉ Omalizumab

Brand Name

Xolair

Generic Name

Omalizumab

Rx

Dosage Forms

Single-use injection, powder for reconstitution

Usage

Treatment of moderate-to-severe persistent allergic asthma (confirmed by a positive skin test or in vitro reactivity to a perennial aeroallergen) in adults and children ≥6 years of age) not controlled with inhaled corticosteroids with elevated IgE levels. Severe allergic asthma inadequately controlled on a high-dose inhaled corticosteroid and inhaled long-acting beta-2 agonists, chronic idiopathic urticaria in children >12 years of age and adults.

Pregnancy Category

The data with Xolair in pregnant women are insufficient to inform on drug risk. The drug does cross the placenta and increases from the first to third trimester. No fetal harm was observed in monkeys given SUB-Q doses up to 10 times the maximum recommended human dose. EXPECT, a prospective observational study, was designed to establish and monitor outcomes in women exposed to omalizumab during pregnancy or within 8 weeks prior to pregnancy. In 169 pregnancies, the incidence of fetal malformations was found to be no higher than rates in the general population with asthma. No patterns of anomalies were observed. Any abnormalities found in the registry are similar to the findings from other studies in pregnant asthma patients and their infants.

Dosing

Asthma

- SUB-Q by healthcare provider only: 75–375 mg injection every 2 to 4 weeks
- Dose is based on pretreatment IgE serum levels (IU/ml) and body weight (kg). Dosing should not be adjusted based on IgE levels taken during treatment or <1 year following discontinuation of therapy; doses should be adjusted during treatment for significant changes in body weight.

Chronic urticaria

- Dosing for chronic idiopathic urticaria is not dependent on IgE levels or body weight
- 150–300 mg SUB-Q every 4 weeks

Adverse Reactions: Most Common

Arthralgia, fatigue, dizziness, headache, local injection-site reactions, pain, upper respiratory tract infections

Adverse Reactions: Rare/Severe/Important

Anaphylactic shock (majority occurs after first dose, but may occur beyond 1 year after beginning treatment), urticaria, angioedema, malignancy, fever, arthralgia, rash, parasitic infections, thrombocytopenia, DVT, TIA, ischemic stroke, eosinophilia and vasculitis, malignancy

Major Drug Interactions

None known

Contraindications

None

Essential Monitoring Parameters

For the treatment of asthma, monitor IgE before initiation of therapy and >1 year following discontinuation of therapy. IgE levels may be elevated up to a year after discontinuation. Levels taken during treatment or for up to a year following treatment cannot be used to guide dosing. Watch for signs/symptoms of anaphylaxis after omalizumab administration.

Counseling Points

- Xolair should be administered by a healthcare professional in a healthcare setting
- Learn the signs and symptoms of anaphylaxis and seek medical care if such symptoms occur
- Do not abruptly discontinue systemic or inhaled corticosteroids upon initiation of omalizumab therapy due to risk of eosinophilia or features of vasculitis consistent with Churg-Strauss syndrome
- Do not change or stop taking any asthma medication unless instructed to do so by your healthcare provider
- Symptoms do not improve immediately after starting treatment

Key Points

- **Black Box Warning:**
  - Anaphylaxis presenting as bronchospasms, hypotension, urticaria or angioedema. It may occur after the first dose but may also occur after subsequent doses. Patients should be monitored closely after administration.
- Do not use to treat acute asthma symptoms or status asthmaticus
- Dosing is based on weight and baseline IgE concentrations in asthma treatment
- Serum IgE can remain elevated up to 1 year after discontinuation of treatment and should not be checked until this time
- Patients should remain under healthcare observation after administration of omalizumab to monitor for anaphylactic symptoms
- A medication guide must be distributed to the patient before administration of omalizumab

REVIEW QUESTIONS

1. Which of the following combination inhaler products contain a long-acting beta-2 agonist and an inhaled corticosteroid?
   a. Glycopyrrolate/formoterol
   b. Tiotropium/olodaterol
   c. Fluticasone/vilanterol
   d. Glycopyrrolate/indacaterol

2. Which of the following has a Black Box Warning for having an increased risk of asthma-related death and, therefore, is contraindicated as monotherapy in the treatment of asthma?
   a. Albuterol
   b. Olodaterol
   c. Fluticasone
   d. Levalbuterol

3. Which of the following medications should patients be counseled on to rinse their mouth after each use, to avoid oral candidiasis?
   a. Mometasone/vilanterol
   b. Aclidinium
   c. Glycopyrrolate
   d. Omalizumab

4. Which of the following used for COPD maintenance treatment, contain a capsule for oral inhalation that is delivered via a dry powder inhaler device?
   a. Seebri Neohaler
   b. Incruse Ellipta
   c. Tudorza Pressair
   d. Stiolto Respimat

5. The most common adverse effects that can occur for this agent are tremors, palpitations, and tachycardia.
   a. Mometasone
   b. Umeclidinium
   c. Glycopyrrolate
   d. Albuterol

6. Which of the following is an indication for an EpiPen?
   a. COPD
   b. Asthma
   c. Anaphylaxis
   d. Congestion

7. What is an important counseling point for an epinephrine auto-injector?
   a. Epinephrine auto-injectors can be administered through clothing, if necessary
   b. If anaphylactic symptoms persist after first dose, a second dose may be administered in 5 to 15 minutes
   c. Place the needle end of the auto-injector perpendicular (right angle) against the middle of the outer thigh. Hold leg firmly.
   d. All of the above

8. Which of the following inhalers, as monotherapy, is indicated for the treatment of asthma?
   a. Glycopyrrolate
   b. Umeclidinium
   c. Salmeterol
   d. Fluticasone

9. Which of the following inhalers produces bronchodilation by blocking acetylcholine at muscarinic receptors, therefore, blocking the direct constrictor effects of acetylcholine on bronchial smooth muscle?

a. Indacaterol
b. Levalbuterol
c. Aclidinium
d. Budesonide

10. Which of the following inhalers must be primed prior to use?

a. Advair Diskus
b. Spiriva
c. Breo Ellipta
d. Striverdi Respimat

11. Which of the following agents can be used as a rescue inhaler for the treatment of acute bronchospasms?

a. Formoterol
b. Levalbuterol
c. Theophylline
d. Tiotropium

12. Which of the following nasal inhalers is available over-the-counter without a prescription?

a. Qnasl
b. Nasonex
c. Atrovent
d. Flonase

13. Which of the following antihistamines has anticholinergic properties and adverse effects?

a. Cetirizine
b. Fexofenadine
c. Hydroxyzine
d. Loratadine

14. Which of the following agents has a risk of anaphylaxis after the injection?

a. Promethazine
b. Omalizumab
c. Epinephrine
d. Theophylline

15. Which of the following would be considered an appropriate therapeutic concentration of theophylline?

a. 1–5 μg/ml
b. 5–10 μg/ml
c. 15–20 μg/ml
d. 20–30 μg/ml

16. Which of the following agents is associated with tachycardia, arrhythmias, and seizures at higher than therapeutic doses?

a. Tiotropium
b. Albuterol
c. Theophylline
d. Loratadine

17. Which of the following inhaled anticholinergic agents are NOT selective to the M3 receptor?

a. Aclidinium
b. Ipratropium
c. Tiotropium
d. Umeclidinium

18. Which agents may cause fatal respiratory depression if used in children under 2 years of age?

a. Albuterol
b. Cetirizine
c. Promethazine
d. Theophylline

19. Which of the following agents may cause severe tissue damage/necrosis if given through intravenous injection?

a. Diphendydramine
b. Omalizumab
c. Promethazine
d. Theophylline

20. Which of the following inhaled long-acting anticholinergics are indicated for the adjunct treatment of asthma?

a. Aclidinium
b. Glycopyrrolate
c. Tiotropium
d. Umeclidinium

21. Which antihistamine also has antiemetic properties and may be used for motion sickness?

a. Cetirizine
b. Fexofenadine
c. Hydroxyzine
d. Loratadine

22. Which agent should not be used in patients with an allergy to tetracaine or procaine?

a. Benzonatate
b. Codeine
c. Hydroxyzine
d. Ipratropium

23. Which agent may cause increased excitability and potential serotonin syndrome if given to a patient on paroxetine?

a. Fluticasone
b. Guaifenesin and dextromethorphan
c. Levalbuterol
d. Promethazine

24. Which of the following contains a schedule II controlled substance?

a. Robitussin AC
b. Mucinex DM
c. Phenergan with codeine
d. TussiCaps

25. Which inhaled agent would be safest to use in a patient on a strong 3A4 inhibitor?

- **a.** Advair
- **b.** Anoro Ellipta
- **c.** Breo Ellipta
- **d.** Symbicort

26. Which agents may increase the risk of worsening narrow-angle glaucoma or urinary retention?

- **a.** Albuterol
- **b.** Fluticasone
- **c.** Guaifenesin
- **d.** Umeclidinium

27. Which agent may be used for the treatment of chronic asthma and allergic rhinitis?

- **a.** Afrin
- **b.** Allegra
- **c.** Flonase
- **d.** Singulair

28. Which agent should not be used for longer than 3 days?

- **a.** Diphenhydramine
- **b.** Levocetirizine
- **c.** Combivent
- **d.** Oxymetazoline

29. Which agent is cleared more rapidly in a patient who is a smoker, which would require a higher dose?

- **a.** Promethazine
- **b.** Hydrocodone
- **c.** Fluticasone
- **d.** Theophylline

30. Which combination agent contains an anticholinergic and long-acting beta-agonist?

- **a.** Breo Ellipta
- **b.** Dulera
- **c.** Stiolto Respimat
- **d.** Tussionex

CHAPTER 14

Topical Products

Susan Kent Romann, PharmD, BCGP

ANALGESICS

Introduction

Capsaicin induces the release of substance P from peripheral sensory neurons. Substance P is the primary mediator of pain impulses from the periphery to the CNS; after repeated application, capsaicin depletes the neuron of substance P and prevents reaccumulation. The lidocaine topical patch offers a unique option for chronic pain syndromes. Systemic adverse reactions with appropriate use are unlikely, due to the small dose absorbed.

Mechanism of Action for the Drug Class

Although the exact mechanism of action has not been fully elucidated, capsaicin is a neuropeptide-active agent that affects the synthesis, storage, transport, and release of substance P. In addition to mediating pain impulses, substance P has also been shown to be released into joint tissues, where it activates inflammatory intermediates that are involved with the development of rheumatoid arthritis. Capsaicin renders skin and joints insensitive to pain by depleting and preventing reaccumulation of substance P in peripheral sensory neurons. With the depletion of substance P in the nerve endings, local pain impulses cannot be transmitted to the brain. With the topical patch, following an initial stimulation of the transient receptor potential vanilloid-1 receptors (TRPV1) and enhanced pain, there is a reduction in TRPV1-expressing nociceptive nerve endings and a reduction in epidermal nerve fiber density resulting in pain reduction. Lidocaine is an amide-type local anesthetic agent. It has been suggested that it stabilizes neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses, producing an analgesic effect.

Members of the Drug Class

In this section: Capsaicin, lidocaine topical patch; Others: Benzyl alcohol, lidocaine (jelly, spray, gel, cream, ointment), methyl salicylate and menthol, trolamine

◉ Capsaicin

Brand Name

Allevess, Capzasin-P, Capzasin-HP, Qutenza, Renovo, Trixaicin HP, Salonpas Gel-Patch Hot

Generic Name

Capsaicin

Rx and OTC

Dosage Forms

Topical cream, gel, liquid, lotion, TD patch

Usage

Temporary treatment of minor muscle and joint pain due to backache, strains, sprains, bruises, cramps, arthritis, or muscle stiffness or soreness; management of neuropathic pain due to diabetic neuropathy or postherpetic neuralgia; treatment of pain associated with psoriasis and intractable pruritus; potential use as topical agent in burning mouth syndrome and oral mucositis

Pregnancy Category B

Dosing

- Muscle/joint pain
  - Cream, gel, liquid, lotion: Apply thin film to affected area 3 to 4 times a day; efficacy may be decreased if used fewer than 3 times a day. Best results are seen after 2 to 4 weeks of continuous use.
  - Patch: Apply one patch to affected area for up to 8 hours (maximum four patches/day); do not use for > 5 consecutive days (product specific)
- Neuropathic Pain
  - Patch (Qutenza 8%): Apply patch to most painful area for 60 minutes. Up to four patches may be placed in a single application. Do not apply more frequently than every 3 months. Pretreat area with topical anesthetic prior to patch application.

Adverse Reactions: Most Common

Application-site reactions of erythema, pain, rash, pruritus. Nausea and nasopharyngitis may also occur.

Adverse Reactions: Rare/Severe/Important

Chemical burns at application site, transient hypertension (reported with transdermal product only)

Counseling Points

- For external use only. Avoid contact with eyes or mucous membranes.
- Wear gloves to apply. Wash hands with soap and water after applying to avoid spreading to eyes or other sensitive areas of the body.
- Do not apply to broken or irritated skin. Do not expose treated area to heat or direct sunlight. Do not apply a bandage to the affected area.
- Transient burning may occur and generally disappears after several days; discontinue use if severe burning develops
  - Topical patch: Apply externally to clean and dry affected area. Remove protective film prior to application. Patch can be cut to the desired size prior to removing protective film (product specific). Do not use within 1 hour before or after bathing. Do not use with a heating pad.
  - Qutenza patch: Patch should only be applied by a healthcare provider. The treatment area must be identified and marked by a physician; may cut patch to desired size and place within 2 hours of opening. Apply using nitrile gloves, not latex. Patch should remain in place for 60 minutes; upon removal, dispose of using biomedical waste procedures.
- Stop use and consult your healthcare provider if redness or irritation develops, symptoms get worse, or symptoms resolve and then recur

Key Points

- Efficacy may be decreased if used fewer than 3 times a day. Best results seen after 2 to 4 weeks of continuous use.
- Mild burning may occur with initial use but should resolve after several days. Discontinue use if severe burning or signs of skin injury (pain, swelling, blistering) occurs.
- Remove topical patches slowly and gently to avoid inhaling airborne material from dried residue; inhalation of airborne capsaicin may result in coughing or sneezing.

◉ Lidocaine Topical Patch

Brand Names

Lidoderm, LidoPatch, Salonpas Lidocaine Pain Relieving Gel patch

Generic Name

Lidocaine

Rx and OTC

Dosage Forms

- Rx: Extended-release 5% topical patch
- OTC: Extended-release 4% topical patch

Usage

Relief of chronic pain in postherpetic neuralgia (PHN); treatment of pain and other chronic pain syndromes, often in an effort to avoid or minimize use of opioid agents and related adverse effects; relief of allodynia (painful hypersensitivity); *temporary relief of localized pain (lidocaine patch)*

Pregnancy Category B

Dosing

- PHN: Apply patch to most painful area after removal from protective envelope. Up to 3 patches may be applied in a single application. Patch may remain in place for up to 12 hours in any 24-hour period. It should only be applied to intact skin.
- Localized pain: Apply OTC patch to painful area. Patch may remain in place for up to 12 hours in a 24-hour period. No more than one patch should be used in a 24-hour period.
- Renal dosage adjustment: Lidocaine is rapidly metabolized in the liver to various metabolites and is excreted by the kidneys. Smaller areas of treatment are recommended in a debilitated patient or a patient with impaired elimination.
- Hepatic dosage adjustment: Lidocaine is rapidly metabolized in the liver to various metabolites and is excreted by the kidneys. Smaller areas of treatment are recommended in a debilitated patient or a patient with impaired elimination.

Adverse Reactions: Most Common

Application-site reactions are generally mild and transient, resolving within minutes to hours

Adverse Reactions: Rare/Severe/Important

Allergic and anaphylactoid reactions associated with lidocaine, although rare, can occur. Transdermal patch may contain conducting metal (e.g., aluminum); remove patch before MRI to avoid burns.

Major Drug Interactions

Local anesthetics: When lidocaine is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered

Drugs Affecting Lidocaine

- Class III antiarrhythmics, beta blockers, conivaptan, CYP1A2/3A4 inhibitors: Increase effect
- CYP1A2/3A4 inducers, herbs with 3A4 induction properties: Decrease effect

Lidocaine's Effect on Other Drugs

- Class III antiarrhythmics, prilocaine: Increases effect; toxic effects are additive and potentially synergistic

Contraindications

Hypersensitivity to another amide-type local anesthetic. Avoid concomitant use with conivaptan.

Essential Monitoring Parameters

Renal and hepatic function

Counseling Points

- Apply to intact skin only
- Patches may be cut into smaller sizes with scissors before removal of the release liner
- If irritation or a burning sensation occurs during application, remove the patch and do not reapply until the irritation subsides
- Wash hands after handling lidocaine and avoid eye contact
- Store and dispose of patches out of the reach of children, pets, and others; do not reuse
- Patches should not be tightly bandaged, used in conjunction with heating pads, or applied to open wounds or sensitive skin
- Report irritation, pain, persistent numbness, tingling, swelling, restlessness, dizziness, acute weakness, blurred vision, ringing in ears, or respiratory difficulty to your healthcare provider

Key Points

- Rx product: Apply up to 3 patches only once for up to 12 hours within a 24-hour period. Patches may be cut to accommodate a smaller area of intact skin.
- Use caution in cases of severe hepatic impairment, in pregnant or nursing women, and in patients prescribed medications to treat irregular heartbeat
- The penetration of lidocaine into intact skin after patch application is sufficient to produce an analgesic effect but less than the amount necessary to produce a complete sensory block
- Remove patch before MRI to avoid burns

ANDROGENS

Introduction

Mechanism of Action for the Drug Class

Testosterone is a naturally occurring androgenic anabolic steroid hormone secreted by the testes. It is the main endogenous androgen responsible for promoting the growth and development of the male sex organs. Testosterone also maintains secondary sex characteristics in men with low levels of androgen.

Members of the Drug Class

Multiple—see comprehensive comparison chart

Rx Only

Class III controlled substances

Dosage Forms

Gel: Nasal, TD; Solution: TD, IM; TD cream, ointment, patch; pellet implant (sub-Q), buccal system

Usage

Male hypogonadism (testosterone deficiency), delayed puberty in males (pediatrics), certain forms of breast cancer in females

Pregnancy Category X

Adverse Reactions: Most Common

Sodium retention, weight gain, HTN, gynecomastia, acne, flushing, contact dermatitis (transdermal patches), local irritation, male pattern baldness

Adverse Reactions: Rare/Severe/Important

Priapism, impaired urination, prostate gland enlargement, sleep apnea, virilization in children and women (due to secondary exposure), polycythemia, edema, hepatotoxicity; remove patch formulations before MRI to avoid burns

Contraindications

Males with breast or prostate cancer; women who are breastfeeding, pregnant, or may become pregnant; hypersensitivity to any ingredient in the respective formulation (i.e., soy, alcohol). Testosterone should not be used for enhancement of athletic performance or in the treatment of erectile dysfunction in men with normal testosterone serum concentrations.

Essential Monitoring Parameters

Confirm hypogonadism prior to starting treatment: AM serum testosterone concentrations on 2 separate days, serum prolactin concentrations, LFTs, blood glucose, lipid panel, HGB, HCT, PSA, and prostate exam; maintenance serum testosterone monitoring varies with each product

Counseling Points

- Follow administration/application technique as instructed by your healthcare provider and per the U.S. Food and Drug Administration (FDA) medication guide that must be dispensed with testosterone products
- Topical solutions and gels: Avoid skin-to-skin transfer of testosterone to another person; thoroughly

Comparison of Testosterone Products (CIII)			
Dosage Form	**Agent**	**Availability**	**Comments**
Oral preparations	Fluoxymesterone (Androxy) Methyltestosterone (Android, Methitest, Testred)	10 mg tab 10 mg cap Methitest: 10 mg tab	**Oral US products:** Not recommended for treatment of androgen deficiency due to ↑ potential for hepatotoxicity
Long-acting parenteral preparations	Testosterone cypionate (Depo-Testosterone, generics) Testosterone enanthate (generics) Testosterone undecanoate (Aveed)	Injection: 100 mg/ml 200 mg/ml Injection: 200 mg/ml Injection: 750 mg/ml	**Pros:** Inexpensive; less frequent IM injections; no dose adjustments (*Aveed*). **Cons:** Frequent IM injections; large volume (*Aveed*); fluctuations in testosterone levels may lead to variations in symptoms. Injection-site pain. *Aveed* is only available through REMS program; prescriber and site must be certified. **Comment:** Follow strict sterile technique; deep IM injection into the gluteal muscle.
Transdermal patch	(Androderm)	Release rate: 2 or 4 mg/24 hours	**Pros:** Convenient to use. Mimics normal diurnal testosterone level changes. **Cons:** Skin reactions occur in over one-third of patients. **Comments:** Apply at the same time each night, immediately upon removal from the protective pouch. Apply to the back, abdomen, upper arms, or thigh. Skin irritation caused by the patch can be treated with a low-potency steroid cream. Rotate administration sites. Avoid showering, washing site, or swimming for ≥ 3 hours after application.
Transdermal gels and solution	(AndroGel) (AndroGel 1.62%) (Fortesta) (Testim) (Vogelxo) (Axiron)	Gel: 1% Gel: 1.62% Gel: 2% Gel: 1% Gel: 1% Solution: 2% 30 mg/1.5 ml	**Pros:** Less skin irritation than patches. Provides normal T levels with minimal fluctuation. **Cons:** Transfer of gel or solution from one person to another (avoid this by washing hands after application and wearing clothing over application site). **Comments:** Do not apply to genitals. Do not apply *Testim* or *Vogelxo* to abdomen. Apply deodorant before *Axiron*, to avoid contamination with the T solution. Bioavailability of *AndroGel 1.62%* is reduced when applied to the abdomen. Avoid showering, washing the site, or swimming for at least 2 to 3 hours after application.
Pellet	(Testopel)	75 mg pellets	**Pros:** Long-acting, convenient. **Cons:** Inflammation and joint pain at pellet site; difficult to adjust dose; pellets can slough out. **Comments:** Approximately 1/3 of material is absorbed in the first month, ¼ in the second month, and 1/6 in the third month.
Buccal system	(Striant)	30 mg buccal tab	**Pros:** Provides therapeutic T levels without large fluctuations. **Cons:** May cause mouth and gum irritation or taste alteration. **Comments:** Not affected by food, tooth brushing, gum chewing, or alcoholic beverages. Should not be chewed or swallowed. Does not dissolve completely. Remove prior to routine morning and evening oral care and prior to placing new buccal system.
Nasal gel	(Natesto)	5.5 mg/pump (7.32 g T)	**Pros:** Less risk for secondary exposure. **Cons:** Inconvenient TID dosing; poorly tolerated with existing nasal allergies or underlying nasal/sinus disease. Can cause rhinorrhea, nasopharyngitis, nasal discomfort, sinusitis, nasal scabbing and nose bleeds. **Comments:** Blow nose prior to use and refrain from blowing nose or sniffing for 1 hour after administration. Temporarily discontinue use with episodes of severe rhinitis.

wash hands after application and cover application site with clothing (i.e., shirt); if secondary exposure occurs, the other person should wash the skin with soap and water as soon as possible
- Dispose of used or unused TD patches by folding adhesive ends together and discard properly away from children or pets
- Use strict sterile technique for IM testosterone injections; SUB-Q implant must be surgically implanted

Key Points

- **Black Box Warnings:**
  - Secondary exposure: Virilization (signs and symptoms of early puberty or development of male characteristics in women) has been reported in children and women who were exposed to topical testosterone gel and solution. Children and women should avoid contact with unwashed or unclothed application sites in men using topical testosterone. Advise patients to strictly adhere to recommended instructions for use.
  - Serious pulmonary oil microembolism (POME) reactions have been reported to occur during or immediately after the administration of testosterone undecanoate injection. These reactions can occur after any injection during the course of therapy, including after the first dose. Symptoms include cough, dyspnea, throat tightening, chest pain, dizziness, syncope, episodes of anaphylaxis. Patients should be observed in a healthcare setting for 30 minutes following each injection in order to provide appropriate treatment, if needed. Due to the risk of POME, testosterone undecanoate is only available under a risk evaluation and mitigation strategy (REMS), called the Aveed REMS Program.
- Prescription testosterone products are FDA-approved as hormone-replacement therapy in men who have low testosterone due to certain medical conditions; use is not recommended for the treatment of erectile dysfunction in men with normal serum testosterone concentrations
- Testosterone products are contraindicated in men with breast or prostate cancer and in women who are breastfeeding, pregnant or may become pregnant (category X)
- An FDA-approved patient medication guide must be dispensed with most testosterone products

ANTIBIOTIC, METRONIDAZOLE

Introduction

Topical metronidazole is a member of the imidazole class of antibacterial agents and is used in the treatment of inflammatory lesions of acne rosacea and bacterial vaginosis

Mechanism of Action for the Drug Class

Metronidazole is classified as an antiprotozoal and antibacterial agent that is active against susceptible organisms. After diffusing into an organism, metronidazole interacts with DNA to cause a loss of helical DNA structure and strand breakage, resulting in inhibition of protein synthesis and cell death in susceptible organisms.

Members of the Drug Class

In this section: Metronidazole
Others: Tinidazole (nitroimidazole)

⦿ Metronidazole

Brand Names

MetroGel, MetroCream, MetroGel-Vaginal, MetroLotion, Noritate, Rosadan, Vandazole

Generic Name

Metronidazole

Rx Only

Dosage Forms

Topical cream, gel, and lotion; vaginal gel

Usage

Treatment of inflammatory papules, pustules, and erythema of acne rosacea; treatment of bacterial vaginosis (BV)

Pregnancy Category B

Dosing

- Topical 0.75%: Apply and rub a thin film twice daily to entire affected area
- Topical 1%: Apply thin film to affected area once daily
- Vaginal:
  - 0.75%: 1 applicatorful (~37.5 mg metronidazole) intravaginally once or twice daily for 5 days. Apply once in morning and evening if using twice daily; if daily, use at bedtime.
  - 1.3%: 1 applicatorful (~65 mg metronidazole) intravaginally as a single dose

Adverse Reactions: Most Common

Burning, skin irritation, dryness, headache; vulva/vaginal irritation, vaginal discharge, fungal infection, ocular burning, and irritation

Adverse Reactions: Rare/Severe/Important

Redness, leukopenia

Major Drug Interactions

Metronidazole's Effect on Other Drugs

- Ethyl alcohol, disulfiram, ritonavir, lopinavir, tipranavir: Enhances adverse/toxic effects
- Warfarin: Oral metronidazole has been reported to potentiate the anticoagulant effect of warfarin, resulting in a prolongation of prothrombin time. The effect of topical metronidazole on prothrombin time is not known.

Contraindications

Vaginal gel: Alcohol use during and for at least 3 days after metronidazole use, concomitant use with or within the last 2 weeks of disulfiram, and hypersensitivity to parabens

Essential Monitoring Parameters

CBC with total and differential leukocyte counts before and after therapy

Counseling Points

- For external use only. Avoid contact with eyes or mouth.
- Wash hands and affected areas before application; wash hands after applying
- Cosmetics may be used after application of topical metronidazole
- Do not engage in vaginal intercourse or use other vaginal products (tampons, douches) during the entire course of therapy with metronidazole vaginal gel. Vaginal intercourse or vaginal products could reduce the efficacy of the gel.
- Discontinue use and notify your healthcare provider at first sign of skin rash or allergic reaction

Key Points

- Follow instructions carefully for topical and vaginal products. Apply thin layer to affected areas; use vaginal applicator as directed by physician; cleanse areas to be treated before topical and vaginal application.
- Avoid contact with eyes
- Monitor for skin rash or allergic reaction
- Disulfiram-like reaction to ethanol may occur with the vaginal gel; consider avoidance of alcoholic beverages during therapy with vaginal gel. Do not administer the vaginal gel to patients who have taken disulfiram within the past 2 weeks.
- Metronidazole is a nitroimidazole and should be used with care in patients with evidence of, or history of, blood dyscrasia

ANTIBIOTIC, MUPIROCIN

Introduction

Mupirocin is an antibiotic produced from *Pseudomonas fluorescens* that is structurally unrelated to any other topical or systemic antibiotics. Mupirocin is used topically in the treatment of impetigo caused by *Staphylococcus aureus* and beta-hemolytic streptococci, including *Streptococcus pyogenes*. Mupirocin is considered a drug of choice for treatment of impetigo, especially when limited numbers of lesions are present.

Mechanism of Action for the Drug Class

Mupirocin reversibly and specifically binds to bacterial isoleucyl transfer RNA synthetase, thereby inhibiting bacterial protein and RNA synthesis. DNA synthesis and cell wall formation are affected to a lesser extent. This agent does not demonstrate in vitro cross-resistance with other classes of antimicrobial agents. Mupirocin is bacteriostatic at low concentrations and bactericidal at high concentrations.

Members of the Drug Class

In this section: Mupirocin
Others: None

◉ Mupirocin

Brand Names

Bactroban, Bactroban Nasal, Centany

Generic Name

Mupirocin

Rx Only

Dosage Forms

Topical cream, ointment; intranasal ointment

Usage

Eradication of nasal colonization with MRSA in adults and pediatric patients ≥12 years of age and healthcare workers (intranasal), treatment of impetigo or secondary infected traumatic skin lesions due to S. aureus and S. pyogenes (topical)

Pregnancy Category B

Dosing

- Impetigo: Apply topical ointment to affected area 3 times a day

- Secondary skin infections: Apply topical cream to affected area 3 times a day for 10 days
- Elimination of MRSA colonization: Approximately one-half of the intranasal ointment from the single-use tube should be applied into one nostril and the other half into the other nostril twice daily (morning and evening) for 5 days
- Renal dosage adjustment: Use with caution in cases of renal impairment

Adverse Reactions: Most Common

Burning, stinging, pruritus, pain, erythema

Adverse Reactions: Rare/Severe/Important

Secondary wound infections

Major Drug Interactions

Mupirocin's Effect on Other Drugs

Live attenuated typhoid vaccine: May decrease level/effect

Essential Monitoring Parameters

Reevaluate patients who have not shown a clinical response within 3 to 5 days of starting therapy (cream or ointment). Watch for evidence of sensitization or severe local irritation.

Counseling Points

- For external use only. Avoid contact with eyes or mouth.
- Use caution in patients with extensive burns or open wounds, because the polyethylene glycol contained in some topical products may be absorbed percutaneously
- Use proper administration technique
- Treated areas may be covered with gauze dressings, if desired
- Notify your healthcare provider of any local side effects, if no improvement is seen in 3 to 5 days, or if signs/symptoms of infection develop
- Patients using the intranasal form should not use other intranasal products concomitantly
- When applied intranasally, drug may cause headache, pharyngitis, or rhinitis

Key Points

- Effective for the treatment of skin lesions due to *S. aureus* and *S. pyogenes* (topical cream) and impetigo (topical ointment) and eradication of nasal MRSA colonization (intranasal ointment)
- Follow appropriate dosing and duration of treatment, depending on the indication
- Be aware of sound-alike/look-alike issues with Bactrim, bacitracin, and baclofen

ANTIBIOTIC, CHLORHEXIDINE GLUCONATE

Introduction

Chlorhexidine gluconate is used topically as an anti-infective skin cleanser for surgical hand antisepsis, preoperative skin preparation, routine hand hygiene in healthcare personnel, and skin wound and general skin cleansing. It is active against gram-positive and gram-negative organisms, facultative anaerobes, aerobes, and yeast.

Mechanism of Action for the Drug Class

The bactericidal effect of chlorhexidine gluconate is a result of the binding of the cationic molecule to negatively charged bacterial cell walls and extramicrobial complexes. At low concentrations, this causes an alteration of bacterial cell osmotic equilibrium and leakage of potassium and phosphorous, resulting in a bacteriostatic effect. At high concentrations, the cytoplasmic contents of the bacterial cell precipitate, resulting in cell death.

Members of the Drug Class

In this section: Chlorhexidine gluconate
Others: Benzalkonium chloride, hexachlorophene

◉ Chlorhexidine Gluconate

Brand Names

Betasept, ChloraPrep, Chlorascrub, Dyna-Hex, Hibiclens, Hibistat

Generic Name

Chlorhexidine gluconate

OTC

Dosage Forms

Applicator, liquid, lotion, solution, sponge, swab, towelette

Usage

Skin cleanser for line placement, skin wounds, preoperative skin preparation; surgical scrub and antiseptic hand rinse for healthcare personnel

Pregnancy Category B or C (manufacturer specific)

Dosing

- Surgical scrub: Scrub 3 minutes and rinse thoroughly; wash for an additional 3 minutes

- Surgical hand antiseptic: Dispense one pumpful in palm of one hand; dip fingertips of opposite hand into solution and work it under nails. Spread remainder evenly over hand and just above elbow, covering all surfaces. Repeat on other hand. Dispense another pumpful in each hand and reapply to each hand up to the wrist. Allow to dry before gloving.
- Hand wash (liquid, solution): Wash with ~ 5 ml for 15 seconds; rinse thoroughly and dry
  - Hand wash (lotion); apply to clean, dry hands and nails. Dispense 1 pumpful (2 ml) into palm of one hand; apply evenly to cover both hands up to the wrists; allow lotion to dry without wiping.
- Towelette: Rub for 15 seconds, paying close attention to nails and between fingers; no rinsing or towel drying necessary
- Preoperative skin preparation
  - Solution: Apply liberally to surgical site and swab for at least 2 minutes; dry with sterile towel and repeat procedure
  - Applicator (ChloraPrep): Completely wet treatment area; use gentle back and forth strokes for 0.5–3 minutes; allow solution to air dry for 1 to 2 minutes or up to 1 hour, depending on surgical site
  - Swab (skin preparation prior to an injection): Apply swab to procedure site for 15 seconds; allow to air dry for 30 seconds

Adverse Reactions: Most Common

Skin erythema, roughness, and/or dryness; sensitization

Adverse Reactions: Rare/Severe/Important

Allergic reactions, anaphylaxis, chemical injury to cornea (with accidental exposure)

Counseling Points

- Keep out of eyes, ears, and mouth
- Avoid use in children < 2 months of age due to increased absorption and/or irritation
- May stain fabrics
- Do not apply to wounds that involve more than superficial layers of skin
- Avoid contact with meninges (do not use on lumbar puncture sites)
- Solutions may be flammable (contain isopropyl alcohol); avoid exposure to open flame and/or ignition sources until completely dry
- Avoid application to hairy areas, which may significantly delay drying time

Key Points

- Note that if used as a disinfectant before midstream urine collection, a false-positive urine protein may result (with dipstick method based on pH indicator color change)
- Chlorhexidine gluconate is used topically as an anti-infective skin cleanser
- Active against gram-positive and gram-negative organisms, facultative anaerobes, aerobes, and yeast
- Follow specific washing times per product for adequate skin cleansing and eradication of bacteria

ANTIBIOTIC, CLINDAMYCIN PHOSPHATE

Introduction

Clindamycin is a semisynthetic derivative of lincomycin and is categorized as a lincosamide antibiotic. It is used topically for the treatment of inflammatory acne vulgaris and intravaginally for the treatment of bacterial vaginosis (BV).

Mechanism of Action for the Drug Class

Clindamycin appears to inhibit protein synthesis in susceptible organisms by binding to 50S ribosomal subunits. The exact mechanism by which clindamycin reduces lesions of acne vulgaris is not fully understood; however, the effect appears to be related to the antibacterial activity of the drug. The drug inhibits the growth of susceptible organisms on the surface of the skin and reduces the concentration of free fatty acids in sebum. Free fatty acids are comedogenic and are believed to be a possible cause of the inflammatory lesions of acne. Clindamycin may be bacteriostatic or bactericidal in action, depending on the concentration of the drug attained at the site of infection and the susceptibility of the infecting organism. Clindamycin phosphate is inactive until hydrolyzed to free clindamycin; phosphatases on the skin rapidly hydrolyze the drug following topical application.

Members of the Drug Class

In this section: Clindamycin phosphate
Others: Benzoyl peroxide, metronidazole, lincomycin

◉ Clindamycin Phosphate

Brand Names

Cleocin, Cleocin-T, Clinda-Derm, Clindagel, ClindaMax, Clindesse, Clindets, Evoclin

Generic Name

Clindamycin phosphate

Rx Only

Dosage Forms

Topical gel, lotion, foam, solution, pledget, vaginal suppository/cream

Usage

Treatment of severe acne (Propionibacterium acnes); treatment of bacterial vaginosis (Gardnerella vaginalis); treatment of susceptible bacterial infections, mainly those caused by anaerobes, streptococci, pneumococci, and staphylococci

Dosing

- Gel (Cleocin T, ClindaMax), pledget, lotion, solution: Apply a thin film twice daily
- Gel (Clindagel), Foam (Evoclin): Apply once daily
- Vaginal suppositories: Insert one suppository (100 mg clindamycin) into vagina once daily at bedtime for 3 days
- Vaginal cream:
  - Cleocin: One applicatorful inserted intravaginally once daily before bedtime for 3 or 7 consecutive days in nonpregnant patients or for 7 consecutive days in pregnant patients
  - Clindesse: One applicatorful inserted intravaginally as a single dose at any time during the day in non-pregnant patients

Adverse Reactions: Most Common

Dryness, burning, itching, scaliness, erythema, or peeling of skin; oily skin; headache; vaginal candidiasis, vaginitis, pruritus, vaginal pain

Adverse Reactions: Rare/Severe/Important

Pseudomembranous colitis, diarrhea, abdominal pain, hypersensitivity reactions, atrophic vaginitis, local edema, menstrual disorders, pyelonephritis, urinary tract infection

Major Drug Interactions

Neuromuscular blocking agents: Clindamycin has been shown to have neuromuscular blocking properties that may enhance the neuromuscular blocking action of other agents. Use with caution in patients receiving such agents, because clindamycin can be absorbed systemically following intravaginal application.

Contraindications

Previous *C. difficile*–associated diarrhea, regional enteritis, ulcerative colitis

Counseling Points

- Topical gel, lotion, or solution: Wash hands thoroughly before applying or wear gloves. Apply thin film of gel, lotion, or solution to affected area. Wash hands thoroughly. Wait 30 minutes before shaving or applying makeup. Shake lotion well prior to use.
- Solution or pledget: Avoid contact with eyes, mouth, or other mucous membranes. Solution/pledget contains an alcohol base; if inadvertent contact with mucous membranes occurs, rinse with liberal amounts of water. Remove pledget from foil immediately before use; discard after single use. May use more than one pledget for each application to cover area.
- Topical foam: Do not dispense directly onto hands or face. Pick up small amounts of foam with fingertips and gently massage into affected areas until foam disappears. Wash hands thoroughly. Wait 30 minutes before shaving or applying makeup.
- Vaginal: Wash hands before using. At bedtime: If using applicator, gently insert full applicator into vagina and expel cream. Wash applicator with soap and water following use. If using suppository, remove foil, and insert high into vagina. Remain lying down for 30 minutes following administration. Avoid intercourse during therapy. Vaginal products may weaken condoms or contraceptive diaphragms. Barrier contraceptives are not recommended concurrently or for 3 to 5 days following treatment (depends on the product).
- Report persistent burning, swelling, itching, excessive dryness, or worsening of condition to your healthcare provider.

Key Points

- Clindamycin is active against *Gardnerella vaginalis* and *Propionibacterium acnes* and is effective in the treatment of bacterial vaginosis and acne vulgaris
- Wash hands thoroughly before applying product or wear gloves

ANTIFUNGALS, IMIDAZOLE DERIVATIVES

Introduction

Ketoconazole and miconazole, synthetic azole antifungal agents, are imidazole derivatives and active against both dermatophytes and *Candida* species. These agents are structurally related to other imidazole-derivative azole antifungal agents.

Mechanism of Action for the Drug Class

These agents alter cell membranes, resulting in increased cell wall permeability, secondary metabolic effects, and growth inhibition. The fungistatic activity of these drugs may result from interference with ergosterol synthesis.

Members of the Drug Class

In this section: Ketoconazole, miconazole
Others: Butoconazole, clotrimazole, econazole, oxiconazole, sertaconazole, sulconazole, tioconazole

◉ Ketoconazole

Brand Names

Extina, Ketodan, Nizoral, Xolegel, Nizoral A-D (OTC)

Generic Name

Ketoconazole

Rx and OTC

Dosage Forms

Cream, foam, gel, shampoo

Usage

Treatment of a variety of cutaneous fungal infections, including cutaneous candidiasis, tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea corporis (ring worm); dandruff; seborrheic dermatitis; tinea (pityriasis) versicolor; OTC labeling: controls flaking, scaling, and itching associated with dandruff

Pregnancy Category C

Dosing

- Fungal infections:
  - Tinea infections: Rub cream gently into the affected and immediate surrounding area once daily for duration of treatment:
    - Tinea corporis: 2 weeks
    - Tinea cruris: 2 weeks
    - Tinea pedis: 6 weeks
  - Tinea versicolor (pityriasis):
    - Apply 2% shampoo to damp skin, lather, leave on 5 minutes, and rinse (one application should be sufficient)
    - Cream: Apply once daily to cover the affected and immediate surrounding area for 2 weeks
- Seborrheic dermatitis:
  - Cream: Rub gently into the affected area twice daily for 4 weeks
  - Foam: Apply to affected area twice daily for 4 weeks
  - Gel: Rub gently into the affected area once daily for 2 weeks
- Dandruff:
  - 1% shampoo (OTC): Apply to wet hair, lather, and rinse thoroughly; repeat. Use every 3 to 4 days for up to 8 weeks, then only as needed to control dandruff

Adverse Reactions: Most Common

Severe skin irritation, pruritus, burning sensation

Adverse Reactions: Rare/Severe/Important

Painful allergic reactions (local swelling and inflammation), contact dermatitis

Counseling Points

- For external use only; not for ophthalmic, oral, or intravaginal use
- Although improvement and symptom relief usually occur within the first week of therapy, tinea corporis and cruris should be treated for 2 weeks
- Tinea pedis should be treated for 6 weeks; cutaneous candidiasis for 2 weeks
- Do not wash topical application sites for at least 3 hours after drug is applied
- Ketoconazole 2% gel or foam is used only for the treatment of seborrheic dermatitis; the safety and efficacy of the foam or gel for the treatment of fungal infections have not been established
- Contact your healthcare provider if severe or persistent adverse effects occur or if the condition worsens

Key Points

- Apply exactly as directed
- Wash hands thoroughly before and after applying
- Keep away from eyes and mouth

◉ Miconazole

Brand Names

Lotrimin AF, Micatin, Baza Antifungal, Carrington Antifungal, Desenex, Micaderm, Podactin, Micro-Guard, Vagistat-3

Generic Name

Miconazole

OTC

Dosage Forms

Aerosol powder/spray, cream, lotion, ointment, powder, solution/tincture, vaginal cream, and suppository

Usage

Treatment of a variety of cutaneous fungal infections, including cutaneous candidiasis, tinea pedis, tinea cruris, tinea corporis, vulvovaginal candidiasis

Pregnancy Category C

Dosing

- Tinea corporis: Apply to affected area twice daily for 4 weeks
- Tinea pedis:
  - Apply to affected area twice daily for 4 weeks
  - Effervescent tablet: Dissolve 1 tablet in 1 gallon of water; soak feet for 15 to 30 minutes; pat dry

- Tinea cruris: Apply to affected area twice daily for 2 weeks
- Vulvovaginal candidiasis:
  - 2% cream: Insert 1 applicatorful at bedtime for 7 days
  - 4% cream: Insert 1 applicatorful at bedtime for 3 days
  - 100 mg suppository: Insert 1 suppository at bedtime for 7 days
  - 200 mg suppository: Insert 1 suppository at bedtime for 3 days
  - 1200 mg suppository: Insert 1 suppository at bedtime or during the day (one-time dose)

Adverse Reactions: Most Common

Burning, irritation, maceration, vulvovaginal burning, irritation, pruritus

Adverse Reactions: Rare/Severe/Important

Allergic contact dermatitis, abdominal cramping

Major Drug Interactions

Drugs Affecting Miconazole

- St. John's wort: May decrease levels

Miconazole's Effect on Other Drugs

- Warfarin: Potential for increased plasma concentrations with intravaginal miconazole; potential for interaction with miconazole applied topically to skin is unknown
- Oral sulfonylureas: May inhibit metabolism

Essential Monitoring Parameter

Diabetic patients should test blood glucose regularly; miconazole may inhibit the metabolism of oral sulfonylureas

Counseling Points

- Wash and dry area before applying medication; apply thinly
- For topical use only; do not get in or near eyes
- If diabetic, test blood glucose regularly; miconazole may inhibit the metabolism of oral sulfonylureas
- Tincture: Patients with diabetes, circulatory problems, or renal or hepatic dysfunction should contact their healthcare provider prior to self-medication
- Cutaneous candidiasis and tinea cruris should be treated for 2 weeks and tinea corporis and pedis for 1 month to reduce the possibility of recurrence
- Miconazole powder or aerosol powder are not recommended for use on the scalp or nails
- Report persistent burning, itching, or irritation to your healthcare provider
- Clinical and mycologic clearing usually occurs after 2 weeks of treatment
- Vaginal products may weaken latex condoms and diaphragms

Key Points

- Apply exactly as directed
- Wash hands thoroughly before and after applying
- Keep away from eyes

ANTIFUNGAL, OXABOROLE

Introduction

Tavaborole is a topical antifungal used to treat onychomycosis of the toenails (tinea unguium, ringworm of the nail). Tavaborole is classified as an oxaborole antifungal agent. Oxaboroles are boron-containing molecules with antifungal activity. The addition of boron into the cyclic structure of a molecule allows for greater stability, improved drug availability at the site of action, and effective target-binding capacity and selectivity. Onychomycosis is a fungal infection of the nails, usually caused by dermatophytes. This toenail fungus often involves several nails and many patients also have tinea pedis (athlete's foot). Left untreated, onychomycosis may lead to progressive destruction and deformity of the affected nails and can spread to other digits and body areas. Onychomycosis is usually treated with an oral antifungal agent, as the use of a topical antifungal alone has been associated with lower cure rates. Although topical antifungals with improved nail penetration are now available (efinaconazole, tavaborole), additional clinical trial data is needed to compare the safety and efficacy of these agents and other topical or oral antifungal agents. Choosing the most appropriate regimen will depend on the severity and extent of nail involvement, organisms involved, reported cure rates, adverse effects, drug interactions, cost and patient/prescriber preferences.

Mechanism of Action for the Drug Class

Tavaborole inhibits fungal protein synthesis by inhibition of an aminoacyl-transfer ribonucleic acid (tRNA) synthetase (AARS). Tavaborole has been shown to selectively inhibit certain fungal enzymes. The shape and small size of boron-based molecules contributes to their ability to reach the site of action.

Member of the Drug Class

Tavaborole

◉ Tavaborole

Brand Name
Kerydin

Generic Name
Tavaborole

Rx Only

Dosage Forms
Solution, external

Usage
Onychomycosis of the toenail(s) due to Trichophyton rubrum and *Trichophyton mentagrophytes*

Pregnancy Category C

Dosing
Apply topical solution to affected toenail(s) once daily for 48 weeks

Adverse Reactions: Most Common
Application site exfoliation, ingrown toenail, application-site erythema, and application-site dermatitis

Counseling Points
- Tavaborole 5% solution is for external use only. Avoid contact with mouth, eyes, and vagina; wash hands with soap and water following application of the drug.
- Do not apply solution to skin other than the skin immediately surrounding treated toenail(s); wipe away excess solution from surrounding skin and allow to dry
- Clean and dry toenail(s) prior to application of the drug; apply the topical solution once daily to completely cover affected toenail(s) using the dropper provided by the manufacturer; also apply under the tip of each affected toenail. Do not use the dropper for any other purpose.
- Tavaborole topical solution is flammable and should not be stored or used near heat or an open flame
- Advise women to inform their provider if they are or plan to become pregnant or breast-feed.

Key Points
- Tavaborole is an oxaborole antifungal topical solution used for the treatment of onychomycosis
- Topical solution should be applied daily for 48 weeks; consult prescriber if local irritation occurs

ANTIFUNGAL, TERBINAFINE

Introduction
Terbinafine is a synthetic allylamine antifungal agent that is structurally and pharmacologically related to naftifine. Compared with azole antifungal agents, terbinafine is more active against dermatophytes and less active against *Candida* species.

Mechanism of Action for the Drug Class
Drugs in this class inhibit squalene epoxidase, a key enzyme in sterol biosynthesis in fungi. This results in a deficiency in ergosterol within the fungal cell wall, resulting in cell death. Terbinafine may be fungicidal or fungistatic in action, depending on the concentration of the drug and the specific fungus tested.

Members of the Drug Class
In this section: Terbinafine
Others: Naftifine

◉ Terbinafine

Brand Name
Lamisil AT, Lamisil Advanced

Generic Name
Terbinafine

Rx (oral tablet) and OTC (topical products)

Dosage Forms
Cream, gel, solution

Usage
Treatment of a variety of cutaneous fungal infections, including tinea pedis; tinea cruris; tinea corporis; tinea versicolor (Canadian prescription formulation)

Pregnancy Category B

Dosing

- Tinea pedis:
  - OTC cream: Apply between the toes to affected area once or twice daily for at least 1 week or apply to the bottom or sides of the feet twice daily for 2 weeks
  - OTC gel: Apply to affected area once daily for at least 7 days
  - OTC solution: Apply to affected area once daily for at least 7 days
- Tinea corporis, tinea cruris:
  - OTC cream: Apply to affected area once daily for at least 1 week
  - OTC gel: Apply to affected area once daily for 7 days
  - OTC solution: Apply to affected area once daily for 7 days

Adverse Reactions: Most Common

Burning, dryness, irritation, pruritus, rash, stinging, tingling

Adverse Reactions: Rare/Severe/Important

Contact dermatitis, exfoliation

Counseling Points

- Cream, gel, and spray are for topical use only; avoid contact with eyes, nose, or mouth
- Wash and dry area thoroughly before applying; apply to affected areas exactly as directed
- Do not use occlusive dressings
- Wash hands after touching the affected areas so that the infection is not spread to other areas of the body or to other individuals
- Do not to use spray solution on the face. If accidental contact with eyes occurs, rinse eyes thoroughly with running water and consult a clinician if symptoms persist.
- Tinea pedis: Wear well-fitting, ventilated shoes and change socks at least once daily
- Report irritation or development of rash to your healthcare provider
- Women of childbearing age should inform their healthcare provider of plans to become pregnant or breastfeed

Key Points

- Apply to affected areas exactly as directed; avoid contact with eyes, nose, mouth, or other mucous membranes
- Thoroughly wash hands before and after application
- Clinical improvement usually is evident within the first week of therapy, and patients usually show continued improvement for several weeks after completion of treatment. Reevaluate diagnosis if no improvement within 2 to 6 weeks of completing therapy.

ANTIFUNGALS, TRIAZOLE DERIVATIVES

Introduction

Terconazole and efinaconazole, triazole derivatives, are synthetic azole antifungal agents. Terconazole is used intravaginally for the treatment of vulvovaginal candidiasis. Terconazole and efinaconazole are structurally similar to imidazole-derivative antifungal agents; however, triazoles have three nitrogens in the azole ring. Terconazole is active against dermatophytes (fungi that require keratin for growth) and *Candida* species. At high concentrations, the drug also has in-vitro activity against some gram-positive and gram-negative bacteria. Efinaconazole is used for the topical treatment of onychomycosis of the toenails (tinea unguium, ringworm of the nail) caused by *Trichophyton rubrum* or *T. mentagrophytes*. Onychomycosis is a fungal infection of the nails usually caused by dermatophytes. This toenail fungus often involves several nails and many patients also have tinea pedis (athlete's foot). Left untreated, onychomycosis may lead to progressive destruction and deformity of the affected nails and can spread to other digits and body areas. Onychomycosis is usually treated with an oral antifungal agent, as the use of a topical antifungal alone has been associated with lower cure rates. Although topical antifungals with improved nail penetration are now available (efinaconazole, tavaborole), additional clinical trial data are needed to compare the safety and efficacy of these agents with other topical or oral antifungal agents. Choosing the most appropriate regimen will depend on the severity and extent of nail involvement, organisms involved, reported cure rates, adverse effects, drug interactions, cost and patient/prescriber preferences.

Mechanism of Action for the Drug Class

Terconazole and efinaconazole are thought to exert their antifungal activity by altering cellular membranes, causing increased permeability and growth inhibition. The mechanism of action may involve inhibition of lanosterol 14-α-demethylase and decreased concentrations of ergosterol in

fungal cell membranes. Depletion of ergosterol affects cell membrane integrity and function and leads to fungal cell death.

Members of the Drug Class

In this section: Efinaconazole, terconazole

Efinaconazole

Brand Name

Jublia

Generic Name

Efinaconazole

Rx Only

Dosage Forms

Solution, external

Usage

Onychomycosis of the toenail(s) due to Trichophyton rubrum and *Trichophyton mentagrophytes*

Pregnancy Category C

Dosing

Apply to affected toenail(s) once daily for 48 weeks

Adverse Reactions: Most Common

Application-site dermatitis, application site vesicles, application site pain, ingrown nail

Counseling Points

- Efinaconazole 10% solution is for external use only. Avoid contact with mouth, eyes, and vagina; Wash hands with soap and water following application of the drug.
- Clean and dry toenail(s) prior to application of the drug; Apply the topical solution once daily using the attached applicator brush and let dry thoroughly
- Avoid pedicures, nail polish and other cosmetic nail products during efinaconazole treatment
- Efinaconazole topical solution is flammable and should not be stored or used near heat or an open flame
- Advise women to inform their provider if they are or plan to become pregnant or breast-feed

Key Points

- Efinaconazole is a topical azole antifungal used for the treatment of onychomycosis
- Topical solution should be applied daily for 48 weeks; consult prescriber if local irritation occurs; avoid pedicures and nail polish for the duration of treatment
- Selection of the most appropriate antifungal regimen will depend on the severity and extent of nail involvement, organisms involved, reported cure rates, adverse effects, drug interactions, cost and patient/prescriber preferences

Terconazole

Brand Names

Terazol 3, Terazol 7

Generic Name

Terconazole

Rx Only

Dosage Forms

Vaginal cream, suppository

Usage

Treatment of uncomplicated vulvovaginal candidiasis

Pregnancy Category C

Dosing

- Vaginal cream 0.4%: Insert 1 applicatorful vaginally at bedtime for 7 consecutive days
- Vaginal cream 0.8%: Insert 1 applicatorful vaginally at bedtime for 3 consecutive days
- Vaginal suppositories: Insert 1 suppository vaginally at bedtime for 3 consecutive days

Adverse Reactions: Most Common

Headache, vulvar/vaginal burning, irritation, or itching

Adverse Reactions: Rare/Severe/Important

Abdominal pain, dysmenorrhea, chills, fever, allergic reactions

Counseling Points

- For vaginal use only
- Open applicator just before administration to prevent contamination; wash applicator after each use with mild soap solution and rinse with water
- Suppository: remove foil packaging prior to insertion; if provided applicator is used for insertion, wash with mild soap and dry thoroughly prior to next dose
- Complete full course of therapy as directed, even during menstruation or if symptoms resolve
- Refrain from intercourse during period of treatment; sexual partner may experience penile irritation
- Suppositories may cause breakdown of rubber/latex products such as condoms and diaphragms; avoid concurrent use
- Inform prescriber of intent to become pregnant or breast-feed
- Report persistent vaginal burning, itching, irritation, or rash to your healthcare provider

Key Points

- Terconazole is a topical azole antifungal agent used intravaginally for the treatment of vulvovaginal candidiasis

- Advise patients to finish complete course, even if symptoms have resolved
- Microbiological studies should be repeated in patients not responding to terconazole to confirm the diagnosis and rule out other pathogens

- Efficacy of intravaginal terconazole is not affected by concomitant use of oral contraceptives
- Administration of intravaginal terconazole does not appear to affect estradiol or progesterone concentrations in women receiving low-dose oral contraceptives

ANTIVIRAL

Introduction

Docosanol 10% cream should be used *only* for symptomatic treatment of herpes labialis, such as perioral herpes, cold sores, and fever blisters in immunocompetent adults and children ≥ 12 years of age. The drug is not indicated for preventive therapy.

Mechanism of Action for the Drug Class

Docosanol is a naturally occurring 22-carbon saturated aliphatic alcohol with antiviral activity against various Herpesviridae, including herpes simplex virus types 1 and 2 (HSV-1, HSV-2). The mechanism of action of docosanol in the treatment of herpes labialis lesions does not involve direct virucidal activity against HSV. Docosanol reduces viral replication and activity by effectively inhibiting the fusion between the plasma membrane and the herpes simplex virus envelope.

Members of the Drug Class

In this section: Docosanol
Others: Acyclovir

◉ Docosanol

Brand Name

Abreva

Generic Name

Docosanol

OTC

Dosage Form

Topical cream

Usage

Topical treatment of recurrent herpes labialis in adults and children ≥ 12 years of age (perioral herpes, cold sores, fever blisters on the face or lips)

Pregnancy Category

Studies have not been conducted, thus fetal risk cannot be ruled out. Consult clinician before use.

Dosing

Herpes simplex (face/lips): Apply topical cream five times a day to affected area of face or lips. Start at first sign of cold sore or fever blister and continue until healed.

Adverse Reactions: Most Common

Application site reactions (burning, stinging), headache

Counseling Points

- Wash hands before and after applying docosanol
- Rub in gently to cover affected area completely; avoid applying directly inside the mouth or around the eyes; do not share product with others
- Use only to treat oral/facial herpes simplex on the lips and face. Do not use on genital herpes lesions.
- May cause application site reactions or headache
- For best results, cosmetics should be removed from the affected areas prior to applying or reapplying docosanol cream
- Cosmetics may be applied to the lips or skin after docosanol cream is applied. To avoid spreading the HSV infection, a separate applicator should be used to apply cosmetics or sunscreen over unhealed lesions.
- Topical docosanol should be discontinued if lesions are not healed after 10 days of treatment. An updated diagnosis and additional treatment may be indicated.
- Women of childbearing age should inform their healthcare provider of plans to become pregnant or breast-feed

Key Points

- Initiate therapy at the earliest sign or symptom of cold sore/fever blister (tingling, pruritus, redness, presence of a bump); best results obtained with early treatment
- Docosanol is only for *symptomatic* treatment of herpes labialis. It is not indicated for preventive therapy.
- Remove makeup or other cosmetic products from affected areas prior to docosanol application
- Secondary bacterial infection may be present if lesions do not heal within 7 to 10 days

CELL STIMULANT AND PROLIFERANT, RETINOID

Introduction

Tretinoin is classified as a retinoid and is used topically for the treatment of acne vulgaris and to minimize the effects of aging on the skin (wrinkles, mottled skin areas, or rough skin areas). Tretinoin therapy has not been shown to cure acne vulgaris, and relapses typically occur within 3 to 6 weeks after the drug is discontinued. Best results are usually seen when treatment is initiated in the early stages of acne vulgaris in which numerous comedones are present. Comedones are small, flesh-colored, white, or dark bumps that give skin a rough texture. These bumps are caused by acne vulgaris. The drug is not effective for the treatment of most cases of severe acne where pustules or cysts have developed; however, it has been suggested that it may be used adjunctively in the management of associated comedones.

Mechanisms of Action for the Drug Class

As a derivative of vitamin A, topical tretinoin modifies epithelial growth and differentiation. In patients with acne, it prevents certain epithelial cells from sticking together and decreases the formation of comedones. It is also thought to stimulate turnover of follicular epithelial cells, causing existing comedones to slough off.

Members of the Drug Class

In this section: Tretinoin
Others: Isotretinoin, clindamycin and tretinoin

◉ Tretinoin

Brand Name

Atralin, Avita, Refissa, Renova, Retin-A, Retin-A Micro, Tretin-X

Generic Name

Tretinoin

Rx Only

Dosage Forms

Cream, gel

Usage

Acne vulgaris, photoaging (palliation of fine wrinkles, hyperpigmentation, and rough facial skin)

Pregnancy Category C

Dosing

- Acne vulgaris: Apply once daily to acne lesions before bedtime or in the evening
- Photoaging: Apply a pea-sized amount of cream to entire face once daily in the evening or before bedtime

Adverse Reactions: Most Common

Temporary feeling of warmth or slight stinging, redness, and scaling of the skin; peeling; dry skin; burning; pruritus; photosensitivity

Adverse Reactions: Rare/Severe/Important

Skin edema, blistering, contact dermatitis, possible worsening of eczema and/or acne

Major Drug Interactions

Drugs Affecting Tretinoin

- Keratolytic agents (benzoyl peroxide, salicylic acid, resorcinol): Possible additive effects
- Photosensitizing agents (fluoroquinolone antibiotics, thiazide diuretics, sulfonamides, tetracyclines, phenothiazines): Increased risk of photosensitivity

Contraindications

Avoid use of photosensitizing agents

Counseling Points

- Prior to application, wash hands; gently wash face with a mild soap; pat dry and wait 20 to 30 minutes
- Apply a thin layer to the affected area in the evening or before bedtime. Avoid contact with the eyes, ears, nostrils, mucous membranes, mouth, or open wounds
- Avoid the use of medicated drying or abrasive facial cleansers, irritating cosmetics, and other processes (electrolysis) that might dry or irritate the skin
- Minimize exposure to sunlight and avoid use of sunlamps; use sunscreen products (SPF 15 or greater) and protective clothing over treated areas when sun exposure cannot be avoided
- Avoid concomitant use of photosensitizing agents
- Gels are flammable; avoid heat, flames, or smoking during use of gel formulations (Retin-A, Avita)
- Women of childbearing age should inform their healthcare provider of plans to become pregnant or breastfeed

Key Points

- Avoid excessive use of topical tretinoin; if a severe reaction occurs, use less frequently, discontinue until skin integrity is restored, or permanently discontinue, depending on the severity of the reaction
- Exposure to UV light increases the intensity of the inflammatory reaction to tretinoin therapy; use sunscreen products to prevent sunburn; tretinoin is not recommended for patients with sunburn until full recovery occurs
- Use with extreme caution in patients with eczema.

COMBINATION ANTIBIOTIC: BACITRACIN, NEOMYCIN, AND POLYMYXIN B

Introduction

Neosporin is a combination antibiotic composed of bacitracin, neomycin, and polymyxin B. Bacitracin is active against many gram-positive organisms, such as staphylococci, streptococci, anaerobic cocci, corynebacteria, and *Clostridia*. It is also active against gonococci, meningococci, and fusobacteria, but not against most other gram-negative organisms. Neomycin is active against many aerobic gram-negative bacteria and some aerobic gram-positive bacteria. The drug is inactive against fungi, viruses, and most anaerobic bacteria. Polymyxin B is a polypeptide antibiotic that has bactericidal activity against nearly all strains of gram negative bacilli, excluding the *Proteus* group. It is not active against gram-positive bacteria, fungi, gram-negative cocci, *Neisseria gonorrhoeae*, and *Neisseria meningitidis*.

Mechanism of Action for the Drug Class

Bacitracin is a polypeptide antibiotic produced by *Bacillus subtilis*. It inhibits bacterial cell wall synthesis by preventing the transfer of mucopeptides into the growing cell wall. Neomycin is an aminoglycoside antibiotic obtained from cultures of *Streptomyces fradiae.* Neomycin is usually bactericidal in action and appears to inhibit protein synthesis in susceptible bacteria by irreversibly binding to 30S ribosomal subunits. Polymyxin B binds to phospholipids and exerts its effect by increasing bacterial cell membrane permeability. In combination, these agents are used for the prevention or treatment of superficial infections of the skin caused by susceptible bacteria.

Members of the Drug Class

In this section: Bacitracin, neomycin, polymyxin B Others: This combination plus hydrocortisone or pramoxine

◉ Bacitracin, Neomycin, and Polymyxin B

Brand Names

Neosporin, Medi-First Triple Antibiotic, Triple Antibiotic

Generic Names

Bacitracin, neomycin, polymyxin B

OTC

Dosage Form

Topical ointment

Usage

Prevention of infection in minor cuts, scrapes, and burns

Pregnancy Category C

Dosing

Apply 1 to 3 times a day to the infected area; may cover with sterile bandage, if necessary

Adverse Reactions: Most Common

Erythema, itching, swelling, irritation

Adverse Reactions: Rare/Severe/Important

Allergic contact dermatitis, failure to heal, anaphylaxis

Contraindications

Mycobacterial or fungal infections

Counseling Points

- For external use only. Keep out of mouth, nose, and eyes. Wash hands before and after use.
- Should not be used for self-medication on deep or puncture wounds, animal bites, or serious burns; not for application to large areas of the body
- Clean affected area before use and dry well; apply a thin layer to affected skin and rub in gently; may cover with dressing, if needed
- Notify healthcare provider if needed for > 1 week

Key Points

- Used for the prevention and treatment of superficial dermal infections; may also minimize appearance of scars
- Wash hands before and after use; not for use in mouth, nose, or eyes
- Do not use > 1 week

COMBINATION ANTIBIOTIC: ERYTHROMYCIN AND BENZOYL PEROXIDE

Introduction

Erythromycin and benzoyl peroxide is a combination topical antibiotic product used for the treatment of acne vulgaris.

Mechanism of Action for the Drug Class

Erythromycin is a macrolide antibiotic that is active against strains of susceptible organisms. Erythromycin inhibits RNA-dependent protein synthesis at the chain-elongation

step; it binds to the 50S ribosomal subunit, resulting in blockage of transpeptidation. Benzoyl peroxide is an antibacterial and keratolytic agent (a substance that promotes the softening and peeling of the epidermis) that releases free-radical oxygen and oxidizes bacterial proteins in the sebaceous follicles, decreasing the number of anaerobic bacteria and irritating-type free fatty acids.

Members of the Drug Class

In this section: Erythromycin and benzoyl peroxide
Others: Clindamycin and benzoyl peroxide, benzoyl peroxide and hydrocortisone

◉ Erythromycin and Benzoyl Peroxide

Brand Names
Benzamycin

Generic Names
Erythromycin, benzoyl peroxide

Rx Only

Dosage Form
Gel

Usage
Treatment of mild-to-moderate acne vulgaris

Pregnancy Category C

Dosing
Adults and children ≥12 years of age: Apply to affected area twice daily, morning and evening

Adverse Reactions: Most Common
Peeling, erythema, edema, dry skin, urticaria

Adverse Reactions: Rare/Severe/Important
Sunburn, bleaching of hair and colored fabric, abdominal pain, cramps, diarrhea

Counseling Points
- For external use only; avoid applying to inside nose, mouth, eyes, and mucous membranes; wash hands before and after use
- Do not use any other topical acne preparation unless otherwise directed by your healthcare provider
- Report any adverse effects or if condition worsens

Key Points
- Clean skin before use; apply twice daily to affected area
- Patients should not use any other topical acne preparation concomitantly
- May bleach hair or colored fabric

COMBINATION: ANTIFUNGAL AND CORTICOSTEROID

Introduction

The combination of clotrimazole and betamethasone is used to treat fungal skin infections, such as athlete's foot, jock itch, and ringworm.

Mechanism of Action for the Drug Class

Clotrimazole is a synthetic antifungal agent that is active against most strains of dermatophytes. Clotrimazole binds to phospholipids in the fungal cell membrane, altering cell wall permeability, which results in the loss of essential intracellular elements. Betamethasone is a synthetic corticosteroid used to relieve redness, swelling, itching, and other discomforts of fungal infections. Betamethasone controls the rate of protein synthesis; depresses the migration of polymorphonuclear leukocytes and fibroblasts; and reverses capillary permeability and lysosomal stabilization at the cellular level to prevent or control inflammation.

Members of the Drug Class

In this section: Clotrimazole and betamethasone dipropionate
Others: Nystatin/triamcinolone

◉ Clotrimazole and Betamethasone Dipropionate

Brand Name
Lotrisone

Generic Name
Clotrimazole and betamethasone dipropionate

Rx Only

Dosage Forms
Cream, lotion

Usage

Treatment of symptomatic inflammatory tinea pedis, tinea cruris, and tinea corporis caused by Trichophyton rubrum, T. mentagrophytes and Epidermophyton floccosum

Pregnancy Category C

Dosing

- Adults ≥ 17 years of age: Massage into affected area twice daily, morning and evening
- Do not exceed application of 45 g of cream per week or 45 ml of lotion per week

Adverse Reactions: Most Common

Itching, skin irritation, dry skin, paresthesia

Adverse Reactions: Rare/Severe/Important

Erythema, drug-induced adrenocortical insufficiency, HPA-axis suppression

Major Drug Interactions

Potential pharmacologic interaction with other corticosteroid-containing preparations

Essential Monitoring Parameters

Periodic HPA-axis suppression tests, especially with prolonged use, use under occlusive dressings, or use over large surface area

Counseling Points

- For external use only. Avoid contact with eyes and mouth.
- Shake lotion well before use
- Use for the full treatment duration, even if symptoms have improved
- Notify your healthcare provider if there is no improvement after 1 week for *tinea cruris* or *tinea corporis* or after 2 weeks for *tinea pedis*
- Do not bandage, cover, or wrap the treated area
- Do not use on open wounds

Key Points

- Clinical improvement usually seen within 1 week for *tinea cruris* and *tinea corporis* and within 2 weeks for *tinea pedis*
- Follow recommended duration of treatment
- This medication should not be used > 2 weeks for *tinea corporis* or *tinea cruris* or > 4 weeks for *tinea pedis*
- This medication is not recommended for the treatment of diaper dermatitis

CORTICOSTEROID: CLOBETASOL PROPIONATE

Introduction

Clobetasol propionate is a very high-potency synthetic fluorinated corticosteroid.

Mechanism of Action for the Drug Class

Following topical application, corticosteroids produce anti-inflammatory, antipruritic, and vasoconstrictor actions. The activity of this class is thought to result at least, in part, from binding with a steroid receptor that controls the rate of protein synthesis. It depresses the migration of polymorphonuclear leukocytes and fibroblasts and reverses capillary permeability and lysosomal stabilization at the cellular level to prevent or control inflammation.

Members of the Drug Class

In this section: Clobetasol propionate
Others: Betamethasone dipropionate 0.05%, fluocinonide 0.1%, halobetasol 0.05%

◉ Clobetasol Propionate

Brand Names

Clobex, Clodan, Cormax, Olux, Temovate

Generic Name

Clobetasol propionate

Rx Only

Dosage Forms

Aerosol (foam), cream, gel, liquid, lotion, ointment, shampoo, solution

Usage

Short-term relief of the inflammatory and pruritic manifestations of moderate-to-severe corticosteroid-responsive dermatoses, including plaque psoriasis and scalp psoriasis; oral mucosal inflammation (unlabeled)

Pregnancy Category C

Dosing

- Apply to affected area twice daily, morning and evening, for up to 2 weeks
- Total dose should not exceed 50 g per week (or 50 ml per week)
  - Spray: Spray directly onto affected area twice daily and gently rub into skin. Limit treatment to 4 consecutive weeks. Total dose should not exceed 50 g/week or 59 ml/week; limit to 26 sprays/application or 52 sprays/day.
- Scalp psoriasis: Apply thin film of shampoo to *dry* scalp once daily; leave in place for 15 minutes; then add water, lather, and rinse thoroughly. Limit treatment to 4 consecutive weeks.

Adverse Reactions: Most Common

Skin burning, tingling, cracking, pruritus, folliculitis, alopecia, headache

Adverse Reactions: Rare/Severe/Important

Acneiform eruptions, allergic contact dermatitis

Contraindication

Primary scalp infections (scalp solution only)

Essential Monitoring Parameters

Periodic HPA-axis suppression tests, especially with prolonged use, use under occlusive dressings, or use over large surface area

Counseling Points

- For external use only; follow specific product directions
- Apply the smallest amount that will cover the affected area. Do not apply to face, groin, or axilla areas. Total dose should not exceed 50 g per week (or 50 ml per week).
- Foam: Turn can upside down and spray a small amount (golf-ball size) of foam into the cap or another cool surface. If fingers are warm, rinse with cool water and dry before handling (foam will melt on contact with warm skin). Massage foam into affected area.
- Spray: Spray directly onto affected area of skin. Gently and completely rub into skin after spraying.

Key Points

- For external use only; avoid contact with eyes or mucous membranes
- Do not apply to face, axilla, or groin areas
- Discontinue when control achieved; treatment beyond 2 consecutive weeks is not recommended (4 weeks for spray and shampoo). Total dosage should not exceed 50 g per week (50–59 ml per week, depending on product).
- The treated skin area should not be bandaged or wrapped unless directed by a physician
- Adverse systemic effects, including hyperglycemia, fluid, and electrolyte changes, and HPA-axis suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing

CORTICOSTEROID: FLUOCINONIDE

Introduction

Fluocinonide is a high- to very-high-potency fluorinated topical corticosteroid, depending on the product formulation

Members of the Drug Class

In this section: Fluocinonide
Others: Betamethasone dipropionate/valerate, desoximetasone, triamcinolone acetonide

◉ Fluocinonide

Brand Names

Vanos

Generic Name

Fluocinonide

Rx Only

Dosage Forms

Very high potency: 0.1% cream; high potency: 0.05% cream, gel, ointment, solution

Usage

Atopic dermatitis, corticosteroid-responsive dermatoses, plaque psoriasis, other inflammatory and pruritic dermatologic conditions

Pregnancy Category C

Dosing

- Pruritus and inflammation (0.05%): Apply thin layer to affected area 2 to 4 times daily, depending on the severity of the condition

- Plaque-type psoriasis (0.1%): Apply a thin layer once or twice daily to affected areas for maximum of 2 consecutive weeks or 60 g per week total exposure

Adverse Reactions: Most Common

Dry skin, pruritus, sensation of burning of skin, headache, nasal congestion

Adverse Reactions: Rare/Severe/Important

Cushing's syndrome, hyperglycemia, adrenal suppression, allergic contact dermatitis

Contraindications

Untreated bacterial infection; skin lesions caused by tuberculosis, fungal, or viral agents, including herpes simplex, vaccinia, and varicella

Essential Monitoring Parameters

HPA-axis suppression should be tested periodically when fluocinonide is applied to large or occluded areas or used on altered skin barriers. It should also be tested in those patients receiving prolonged therapy or concomitant steroids or in those with liver failure.

Counseling Points

- For external use only. Avoid exposure to eyes, mucous membranes, or open wounds.
- Topical (0.1% cream): Affected area should be limited to < 10% of body surface area. Not recommended for use > 2 weeks or > 60 g per week total exposure.
- Use exactly as directed and for no longer than the period prescribed
- Before using, wash and dry area gently. Apply in a thin layer.
- Do not use occlusive dressing unless advised by prescriber. Avoid prolonged or excessive use around sensitive tissues or the genital or rectal areas.
- Avoid exposing treated area to direct sunlight
- Inform your healthcare provider if condition worsens or fails to improve

Key Points

- Therapy should be discontinued when control is achieved. If no improvement is seen, reassessment of diagnosis may be necessary.
- Not for ophthalmic use (0.05% cream, ointment)
- The 0.1% formulation should not be used on the face, groin, or axilla
- Use of the 0.1% formulation for > 2 weeks is not recommended

CORTICOSTEROID: HYDROCORTISONE

Introduction

Hydrocortisone is a low-to-medium potency corticosteroid used for the relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses

Members of the Drug Class

In this section: Hydrocortisone
Others: Desonide, fluocinolone acetonide, mometasone (low-to-medium potency)

◉ Hydrocortisone

Brand Names

Various (Anusol-HS, Cortaid, Cortenema, Dermasorb HC, Proctocort, Westcort)

Generic Name

Hydrocortisone

Rx and OTC

Dosage Forms

Topical cream, gel, lotion, ointment, paste, solution, foam; rectal cream, foam, suppository, suspension enema

Usage

Minor skin irritations; itching and rash due to eczema, dermatitis, insect bites, poison ivy, poison oak, poison sumac, soaps, detergents, cosmetics, or jewelry; late phase of allergic contact dermatitis; scalp dermatitis; seborrheic or atopic dermatitis; psoriasis; adjunctive treatment of ulcerative colitis; anogenital pruritus; proctitis; inflamed hemorrhoids; oral lesions (hydrocortisone acetate paste)

Pregnancy Category C

Dosing

- Skin dermatoses: Apply appropriate product sparingly 1 to 4 times daily; apply aerosol foam to affected area 2 to 4 times daily
- Scalp dermatoses: Part the hair and apply small amount of lotion or solution directly to the affected area; rub gently into scalp. Maintain usual hair care, but do not wash out lotion immediately after application. Alternatively, apply aerosol to dry scalp after shampooing.
- Anal/genital itching (OTC labeling): Apply to affected area up to 3 to 4 times/day

- Hemorrhoids: Remove foil and insert one suppository rectally (25 or 30 mg) twice daily for 2 weeks
- Ulcerative colitis:
  - Foam: Insert one applicatorful (90 mg) 1 to 2 times daily for 2 to 3 weeks, then every other day; taper dose to discontinue long-term therapy
  - Suspension: Insert 1 enema (100 mg) every night for 21 days or until remission; may require 2 to 3 months of therapy; Gradually reduce administration to every other night for 2 or 3 weeks to discontinue long-term therapy
- Oral lesions: Press a small amount of paste to the lesion without rubbing until a thin film develops 2 or 3 times daily after meals and at bedtime

Adverse Reactions: Most Common

Eczema, pruritus, stinging, dry skin, folliculitis, acneiform eruptions, hypertrichosis

Adverse Reactions: Rare/Severe/Important

Allergic contact dermatitis, burning, HPA-axis suppression, hypopigmentation, skin atrophy, secondary infection, perioral dermatitis, metabolic effects

Contraindications

Rectal enema is contraindicated with systemic fungal infections and ileocolostomy during the immediate or early postoperative period. Cortifoam is also contraindicated with obstruction, abscess, perforation, peritonitis, fresh intestinal anastomoses, extensive fistulas, and sinus tracts (other enemas are labeled to be used with caution).

Essential Monitoring Parameter

HPA-axis suppression should be tested periodically when hydrocortisone is applied to large or occluded areas or used on altered skin barriers. It should also be tested in those patients receiving prolonged therapy or concomitant steroids.

Counseling Points

- For dermatologic use only; avoid contact with eyes
- Hydrocortisone and its acetate, buteprate, butyrate, and valerate esters are applied topically
- Nonprescription preparations should not be used for self-medication for >7 days; when used for self-medication, do not use for diaper dermatitis
- If the condition worsens or symptoms persist, discontinue, and consult your healthcare provider
- Before applying, wash area gently and thoroughly; apply a thin film to cleansed area and rub in gently until medication vanishes
- Reserve occlusive dressings for severe or resistant dermatoses as directed by your healthcare provider
- Avoid exposing affected area to sunlight
- Administer retention enema, suppository, or foam carefully according to manufacturer's instructions

Key Points

- Consider location of the lesion and the condition being treated when choosing a dosage form
- Creams are suitable for most dermatoses, but ointments may also provide some occlusion and are generally used for the treatment of dry, scaly lesions
- Lotions are best for treatment of weeping eruptions, especially in areas subject to chafing. Lotions, gels, and aerosols may be used on hairy areas, particularly the scalp.
- Patients applying a topical corticosteroid to a large surface area and/or to areas under occlusion should be evaluated periodically for evidence of HPA-axis suppression

CORTICOSTEROID: MOMETASONE FUROATE

Introduction

Mometasone furoate is a synthetic, nonfluorinated, medium-potency topical corticosteroid that has anti-inflammatory, antipruritic, and vasoconstrictive properties. Mometasone is a derivative of prednisolone and differs structurally from beclomethasone. The structural differences are thought to enhance the topical anti-inflammatory activity of mometasone.

Members of the Drug Class

In this section: Mometasone furoate
Others: Hydrocortisone butyrate 0.1%, hydrocortisone valerate 0.2%, betamethasone valerate 0.1% cream; fluocinolone acetonide 0.025% (medium potency)

◉ Mometasone Furoate

Brand Name

Elocon

Generic Name

Mometasone furoate

Rx Only

Dosage Forms

Cream, lotion, ointment

Usage

Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses

Pregnancy Category C

Dosing

Apply thin film (cream, ointment) or a few drops (lotion) to affected areas once daily

Adverse Reactions: Most Common

Burning, pruritus, stinging/tingling

Adverse Reactions: Rare/Severe/Important

Dryness, irritation, skin atrophy, bacterial skin infection, skin depigmentation

Essential Monitoring Parameters

HPA-axis suppression should be tested periodically when mometasone furoate is applied to large or occluded areas

Counseling Points

- For external use only. Avoid contact with eyes, mouth, and open wounds.
- Avoid prolonged or excessive use around sensitive tissues, underarms, or the genital or rectal areas (including the diaper area)
- Wash and dry affected area gently before applying product; apply sparingly
- Report severe or persistent adverse effects or if no improvement in 2 weeks to your healthcare provider
- Discontinue use and notify your healthcare provider at the first sign of allergic reaction or skin rash
- The treated skin area should not be covered with any occlusive dressing

Key Points

- Topical mometasone furoate products are applied sparingly in thin films and are rubbed into the affected area, usually once daily
- The treated skin area should not be covered with any occlusive dressing because this can increase percutaneous penetration of mometasone

CORTICOSTEROID: TRIAMCINOLONE ACETONIDE

Introduction

Triamcinolone acetonide is a medium- to high-potency synthetic fluorinated corticosteroid that has anti-inflammatory, antipruritic, and vasoconstrictive properties

Members of the Drug Class

In this section: Triamcinolone acetonide
Others: Betamethasone valerate, hydrocortisone valerate, fluocinolone acetonide

◉ Triamcinolone Acetonide

Brand Names

Kenalog, Triderm

Generic Name

Triamcinolone acetonide

Rx Only

Dosage Forms

Aerosol, cream, lotion, ointment, paste

Usage

Inflammatory dermatoses responsive to steroids, including contact/atopic dermatitis; adjunctive treatment and temporary relief of symptoms associated with oral inflammatory lesions and ulcerative lesions resulting from trauma

Pregnancy Category C

Dosing

- Cream, ointment: Apply thin film to affected area 2 to 4 times a day, depending on severity
  - Lotion:
    - 0.025%: Apply thin film to affected areas 3 to 4 times a day
    - 0.1%: Apply thin film to affected areas 2 to 4 times a day
- Spray: Apply to affected area 3 to 4 times a day
- Oral topical: Press a small amount (about 0.25 inch) to the lesion without rubbing until a thin film develops; apply at bedtime and, if necessary, 2 or 3 times daily after meals

Adverse Reactions: Most Common

Dryness, burning, itching, irritation, folliculitis

Adverse Reactions: Rare/Severe/Important

Acneiform eruptions, allergic contact dermatitis, secondary skin infection, skin atrophy

Contraindications

Fungal, viral, or bacterial infections of the mouth or throat (oral topical formulation)

Essential Monitoring Parameters

Periodic HPA-axis suppression tests, especially with prolonged use, use under occlusive dressings, or use over large surface area

Counseling Points

- For external use only. Do not apply to eyes, mucous membranes, or open wounds.
- Oral topical: Apply at bedtime or after meals, if applications are needed throughout the day. Do not use if fungal, viral, or bacterial infections of the mouth or throat are present. If lesion has not improved in 7 days, notify your healthcare provider.
- Ointment: Apply a thin film sparingly. Do not use on open skin or wounds. Do not occlude area unless directed.
- Spray: Avoid eyes and do not inhale if spraying near face. Occlusive dressing may be used if instructed. Monitor for infection.

Key Points

- Follow specific product directions for application; for external use only
- Triamcinolone acetonide 0.5% cream, ointment: high-range potency
- Triamcinolone acetonide 0.025%, 0.1% cream, lotion, ointment: medium-range potency
- Generally, most effective in acute or chronic dermatoses (seborrheic or atopic dermatitis, localized neurodermatitis, anogenital pruritus, psoriasis, late phase of allergic contact dermatitis, inflammatory phase of xerosis)
- Avoid eyes, mucous membranes, or open wounds
- Avoid prolonged or excessive use around sensitive tissues or the genital or rectal areas
- Inform your healthcare provider if condition worsens (skin irritation/contact dermatitis) or fails to improve

Comparison of Topical Corticosteroids

Topical steroids are classified based on their vasoconstrictor properties on the skin and ranked on a potency scale of I to VII. Generally, group I is classified as very high potency; II is considered high potency; III, IV, and V are medium potency; VI and VII are low potency. The following chart compares currently available topical steroids.

Potency Group	Corticosteroid	Strength
Very High Potency (I)	Betamethasone dipropionate, augmented	0.05%
	Clobetasol propionate	0.05%
	Fluocinonide	0.1%
	Flurandrenolide	4.0 μg/cm^2
	Halobetasol propionate	0.05%
High Potency (II)	Amcinonide	0.1%
	Betamethasone dipropionate	0.05%
	Desoximetasone	0.25%, 0.05%
	Diflorasone diacetate	0.05%
	Fluocinonide	0.05%
	Halcinonide	0.1%
High Potency (III)	Amcinonide	0.01%
	Betamethasone dipropionate	0.05%
	Betamethasone valerate	0.12%, 0.1%
	Desoximetasone	0.05%
	Diflorasone diacetate	0.05%
	Fluocinonide	0.05%
	Fluticasone propionate	0.005%
	Mometasone furoate	0.1%
	Triamcinolone acetonide	0.05%
Medium Potency (IV)	Betamethasone dipropionate	0.05%
	Clocortolone pivalate	0.1%
	Fluocinolone acetonide	0.025%
	Flurandrenolide	0.05%
	Hydrocortisone valerate	0.2%
	Mometasone furoate	0.1%
	Triamcinolone acetonide	0.1% (0.2 mg per 2-second spray)

Lower-Mid Potency (V)	Betamethasone dipropionate	0.05%
	Betamethasone valerate	0.1%
	Desonide	0.05%
	Fluocinolone acetonide	0.025%
	Flurandrenolide	0.05%
	Fluticasone propionate	0.05%
	Hydrocortisone butyrate	0.1%
	Hydrocortisone probutate	0.1%
	Hydrocortisone valerate	0.2%
	Prednicarbate	0.1%
	Triamcinolone acetonide	0.1%, 0.025%
Low Potency (VI)	Alclometasone dipropionate	0.05%
	Betamethasone valerate	0.1%
	Desonide	0.05%
	Fluocinolone acetonide	0.01%
	Triamcinolone acetonide	0.025%
Least Potent (VII)	Hydrocortisone (base, ≥ 2%)	2.0 or 2.5%
	Hydrocortisone (base, < 2 %)	0.5%, 1.0%
	Hydrocortisone acetate with pramoxine 1% combination	1.0 or 2.5%

PEDICULICIDE AND SCABICIDE

Introduction

Permethrin, a pyrethroid, is active against a broad range of pests, including lice, ticks, fleas, mites, and other arthropods. Permethrin is active against *Pediculus humanus var. capitis* (the head louse) and its nits (eggs); *Phthirus pubis* (the pubic or crab louse) and its nits; and *Sarcoptes scabiei*, the causative parasite of scabies. Permethrin has the advantages of a low potential for toxicity and good ovicidal activity; however, widespread resistance to permethrin has been reported in other countries and the prevalence of resistance to the drug in the United States is unclear.

Mechanism of Action for the Drug Class

Like natural pyrethrins, permethrin acts as a neurotoxin by depolarizing the nerve cell membranes of parasites. The drug disrupts the sodium channel current by which membrane repolarization is regulated. Delayed repolarization results in paralysis of the nerves in the exoskeletal respiratory muscles of the parasite, leading to death. At a concentration of 1%, permethrin is pediculicidal; concentrations of 5% also are scabicidal. Permethrin is rapidly metabolized by ester hydrolysis to inactive metabolites, which are excreted primarily in the urine.

Members of the Drug Class

In this section: Permethrin
Others: Benzyl alcohol, benzyl benzoate, crotamiton, ivermectin, lindane, malathion, pyrethrins/piperonyl butoxide, spinosad

Permethrin

Brand Names

A200 Lice, Elimite, Nix Complete Lice Treatment System, Nix Creme Rinse Lice Treatment, Nix Creme Rinse, Nix Lice Control Spray

Generic Name

Permethrin

Rx and OTC

Dosage Forms

Rx: 5% topical cream; OTC: 1% topical liquid, lotion, solution

Usage

Single-application treatment of infestation with Pediculus humanus var. capitis (head louse) and its nits or Sarcoptes scabiei (scabies); indicated for prophylactic use during epidemics of lice

Pregnancy Category B

The amount of permethrin available systemically following topical application is ≤ 2%. No adequate, controlled studies using topical permethrin in pregnant women have been conducted; thus, use during pregnancy only when clearly needed. The CDC considers permethrin 5% a drug of choice for the treatment of pediculosis or scabies in pregnant or lactating women. Pregnant women should be advised to consult their healthcare provider before self-medicating with topical permethrin.

Dosing

- Head lice in adults and children > 2 months of age: Shampoo hair and rinse with water, towel dry, apply permethrin to scalp, leave on 10 minutes, rinse with warm water; remove nits with nit comb; repeat application if live lice or nits present 7 days after initial treatment.
- Scabies:
  - Apply a generous amount of cream from head to feet, leave on for 8 to 14 hours, wash with soap/water
  - Repeat application if living mites are present 14 days after initial treatment
  - For infants and the elderly, also apply on the hairline, neck, scalp, temple, and forehead

Adverse Reactions: Most Common

Pruritus, erythema, rash, stinging, tingling, numbness or scalp discomfort, edema

Contraindication

Permethrin lotion is contraindicated for use in infants < 2 months of age

Counseling Points

- For external use only. Do not apply to face and avoid contact with eyes or mucous membranes.
- Clothing and bedding must be washed in hot water or dry cleaned to kill nits. May need to treat all members of household and all sexual contacts concurrently. Wash all combs and brushes with permethrin and rinse thoroughly.
- Because scabies and lice are so contagious, use caution to avoid spreading or infecting oneself; wear gloves when applying; one application for scabies is usually curative.
- Apply a sufficient volume of creme rinse to saturate hair and scalp; also apply behind the ears and at the base of the neck. Shake cream rinse well before using.
- Contact your healthcare provider if pruritus, edema, erythema, or stinging or burning of skin occurs; if condition persists; or if skin becomes infected
- Pregnant women should be advised to consult their healthcare provider before self-medicating with topical permethrin

Key Points

- Follow proper application technique, depending on affected body site
- Wear gloves when applying to avoid spreading or becoming infected
- Consider treatment for all household members and sexual contacts
- Wash clothes, bedding, and personal items in hot, soapy water to prevent reinfection

REVIEW QUESTIONS

1. Which of the following antifungal agents contains boron?

a. Kerydin
b. Terazol
c. Jublia
d. Xolegel

2. Which of the following testosterone products should be applied to the scrotum at bedtime?

a. Androderm
b. Testim
c. Axiron
d. Testopel
e. None of the above

3. Which of the following topical analgesic products works by preventing reaccumulation of Substance P in peripheral sensory neurons?

a. LidoDerm
b. Renovo
c. Olux
d. Bactroban

4. Which of the following "generic name–brand name" pairs are not correctly matched??

a. Metronidazole–Vandazole
b. Clindamycin phosphate–Evoclin
c. Clobetasol propionate–Vanos
d. Permethrin–Elimite

5. Which of the following is indicated for the treatment of onychomycosis?

a. Terconazole
b. Miconazole
c. Efinaconazole
d. Clotrimazole

6. Which of the following is a combination product containing an antifungal agent plus a corticosteroid?

a. Temovate
b. Elocon
c. Kenalog
d. Lotrisone

7. Which of the following statements regarding treatment for head lice and scabies is true?
   a. Permethrin has a high potential for toxicity
   b. At a concentration of 1%, permethrin is scabicidal
   c. One application for scabies is usually curative
   d. Permethrin lotion can be used in infants < 2 years of age

8. Which of the following statements is true regarding treatment for hypogonadism in men?
   a. Serum testosterone monitoring is the same for each product
   b. Secondary exposure to topical testosterone can lead to virilization in children and women
   c. Oral testosterone products are the drugs of choice for hypogonadism
   d. Testosterone therapy is recommended in men with erectile dysfunction who have normal serum testosterone concentrations

9. Which of the following is recommended in the treatment of impetigo?
   a. Centany
   b. MetroGel
   c. Axiron
   d. Nizoral

10. Which of the following can be used to treat bacterial vaginosis (BV)?
   a. Metronidazole
   b. Miconazole
   c. Clindamycin phosphate
   d. Terconazole
   e. A and C

11. A 20-year-old female presents with a prescription for ciprofloxacin (a fluoroquinolone antibiotic) to treat a urinary tract infection. You notice a recent prescription for Retin-A on her profile. What is your concern with these 2 prescriptions?
   a. Her insurance won't cover both prescriptions
   b. She should be taking a vitamin A supplement to increase absorption of Retin-A
   c. She has an increased risk of photosensitivity with this combination
   d. She should increase to twice daily application of Retin-A while on the antibiotic

12. All of the following are high potency corticosteroids except?
   a. Betamethasone dipropionate 0.05% ointment
   b. Fluocinonide 0.05% solution
   c. Amcinonide 0.1% ointment
   d. Hydrocortisone valerate 0.2% ointment

13. Which of the following antibiotics are ingredients found in Neosporin?
   a. Bacitracin, neomycin
   b. Bacitracin, neomycin, polymyxin B
   c. Neomycin, polymyxin B
   d. Bacitracin, neomycin, polymyxin B, pramoxine

14. What pregnancy category is Striant?
   a. Pregnancy category B
   b. Pregnancy category C
   c. Pregnancy category D
   d. Pregnancy category X

15. All of the following are potential adverse effects of capsaicin topical patch except:
   a. Hypotension
   b. Nasopharyngitis
   c. Chemical burn at application site
   d. Nausea

16. Which of the following is a true statement regarding lidocaine topical patch use?
   a. Lidocaine patches are available via prescription only
   b. Lidocaine patches can be cut into smaller sizes if necessary
   c. Lidocaine patches can be reused within 12 hours of application
   d. Lidocaine patches can be used with a heating pad for severe pain

17. Drug interactions associated with topical metronidazole include all of the following except:
   a. Topical metronidazole may increase the levels or effects of alcohol
   b. Topical metronidazole may increase the levels or effects of lopinavir
   c. Topical metronidazole may increase the levels or effects of disulfiram
   d. Topical metronidazole is known to prolong prothrombin time in patients receiving warfarin

18. Chlorhexidine gluconate is used topically as a skin cleanser. It is effective against all of the following except:
   a. Fungi
   b. Yeast
   c. Gram-positive organisms
   d. Facultative anaerobes

19. All of the following products are indicated for the treatment of acne vulgaris and/or more severe acne cases caused by *Propionibacterium acnes* except:

- **a.** Erythromycin and benzoyl peroxide
- **b.** Clindamycin phosphate
- **c.** Tretinoin
- **d.** Lindane

20. Which of the following prescriptions for terconazole is correct?

- **a.** Insert 1 applicatorful vaginally at bedtime for 7 days
- **b.** Insert 2 applicatorfuls vaginally at bedtime for 3 days
- **c.** Insert 1 suppository vaginally in the morning and evening for 3 days
- **d.** Insert 1 suppository vaginally at bedtime for 7 days

21. Which of the following is the generic name for Abreva?

- **a.** Miconazole
- **b.** Docosanol
- **c.** Clobetasol
- **d.** Desonide

22. Which of the following is considered a medium-potency corticosteroid?

- **a.** Cortaid
- **b.** Olux
- **c.** Elocon
- **d.** Vanos

23. A high-school football player comes into the pharmacy complaining of itching and burning in the groin area that seems to get worse after football practice. You recognize these symptoms as tinea cruris, or jock itch. Which of the following should you recommend?

- **a.** Lamisil AT cream: Apply to affected area once daily for 7 days
- **b.** Ketodan: Rub foam gently into the area once daily for 6 weeks
- **c.** Micatin: Apply to affected area twice daily for 4 weeks
- **d.** Lotrisone: Massage cream into affected area once daily in the evening

24. Tinea unguium, or ringworm of the nail, is characterized by all of the following except:

- **a.** Patients may be coinfected with tinea pedis (athlete's foot)
- **b.** If untreated, tinea unguium can cause deformity of the affected nail and spread
- **c.** It is a bacterial infection caused by dermatophytes
- **d.** Newer topical agents may have improved nail penetration

25. Which of the following drug: mechanism of action pairs is *incorrect*?

- **a.** Kerydin–Inhibits fungal protein synthesis by inhibition of tRNA synthetase
- **b.** MetroGel–Promotes the growth and development of male sex organs
- **c.** Jublia–Causes decreased concentrations of ergosterol in fungal cell membranes, leading to cell death
- **d.** Nix–Acts as a neurotoxin by depolarizing the nerve cell membranes of parasites

26. Benzamycin can be used to treat mild-to-moderate acne vulgaris; which of the following is *not* a common adverse effect of this product?

- **a.** Bleaching of hair
- **b.** Edema
- **c.** Peeling
- **d.** Constipation

27. Hydrocortisone is indicated for all of the following conditions except:

- **a.** Proctitis
- **b.** Psoriasis
- **c.** Poison sumac
- **d.** Prostatitis

28. The correct dosing of Bactroban to eradicate MRSA colonization is:

- **a.** Apply to affected area 3 times per day
- **b.** Apply to affected area 3 times per day for 10 days
- **c.** Apply small amount into each nostril twice daily for 5 days
- **d.** Apply to affected area every morning and evening for 7 days

29. All of the following are correct regarding the application of permethrin except:

- **a.** Consider treatment of all household contacts and sexual partners
- **b.** Apply a generous amount from head to feet, leave on body overnight, then wash with warm water
- **c.** For infants and the elderly, also apply to the hairline, neck, scalp, temple, and forehead
- **d.** Apply to wet, towel-dried scalp; leave on for 10 minutes, rinse and remove nits with comb

30. Fluocinonide is also known as:

- **a.** Vanos
- **b.** Olux
- **c.** Temovate
- **d.** Kenalog

CHAPTER 15

Natural Products, Dietary Supplements, and Nutrients

Patrick McDonnell, PharmD, FASHP

GENERAL STATEMENT: NATURAL PRODUCTS, DIETARY SUPPLEMENTS, AND NUTRIENTS

Herbs and botanicals have been used for centuries for the treatment and prevention of disease. Egyptian papyruses, as well as Babylonian stone tablets, list "prescriptions" for certain herbals remedies.

These products, defined legally as *dietary supplements* in the United States and referred to as *natural health products* in the United States and Canada, consist of single or many ingredients. Under the Food and Drug Administration's (FDA) 1994 Dietary Supplement Health and Education Act, a *dietary supplement* is defined as a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet. The dietary ingredients in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Although far from complete, data on the safety and efficacy of individual ingredients are more comprehensive for nutrients, such as vitamins, than for herbals and other botanicals. Note that in the United States, these products, which number in the thousands, are marketed with limited regulatory oversight. For example, these products are not monitored for product safety, efficacy, or quality. However, the FDA does regulate the labeling and types of claims made on these products.

This chapter presents some of the most commonly used dietary supplement ingredients. The available products that contain each ingredient are too numerous to list beyond a few examples from the U.S. marketplace. Indications listed are common uses and are not necessarily supported by clinical evidence. Dosing ranges for nutrients are based on the highest Dietary Reference Intake (DRI) level for nonpregnant, nonlactating adults. Dosing for other ingredients is based more on current usage than on dose-finding trials. Additionally, dosing of an ingredient may differ among the products containing them and may not necessarily be well supported in the literature. Although generally well tolerated, dietary supplement products can produce adverse effects and interactions. These are based predominantly on case reports and may be reflective of the ingredient itself or the quality of the product in which it is delivered. Dietary supplement ingredients do not receive formal pregnancy category ratings, and in most cases, they have not been evaluated in pregnancy or lactation. Patients should always consult with their healthcare provider before taking any nonprescription medication or herbal/dietary supplement.

BITTER ORANGE

Introduction

Natural supplements were and still are very popular for weight loss, and consumers are under the assumption that since they are natural, it is a safe way to lose weight. In 1999, the FDA banned weight loss products that contained the natural herbal product, ma huang, also known as ephedra, when they received 140 spontaneous reports of serious and even fatal adverse cardiovascular events in primarily younger consumers who used these products for energy and weight loss. With the removal of ephedra, manufacturers substitute the supplement bitter orange into their products. Bitter orange contains the sympathomimetic compound called synephrine and when used in combination with other sympathomimetics that are perceived safe, such as caffeine, Garcinia cambogia, and others, may lead to unwanted over stimulation of the sympathomimetic nervous system, resulting in potential cardiovascular effects that can be dangerous.

Mechanism of Action for the Drug Class

Bitter orange contains biologically active adrenergic amines, namely synephrine. The effects of synephrine

affects human metabolism by stimulating lipolysis, raising the metabolic rate, and enhancing fat oxidation through increased thermogenesis.

Bitter Orange

Brand Names

Bitter Orange is found as an ingredient in branded products, such as Hydroxycut, Stacker II "Ephedra Free," Dexatrim Max, TNT Fat Burner, Miracle Burn, and numerous others.

Generic Names

Bitter orange, *Citrus aurantium,* bigarade, green orange, kijitsu, laranja-amarga, sour orange, zhi qiao, zhi shi

OTC

Dosage Forms

Tablet, capsule, powdered extracts (also commonly in multi-ingredient supplements)

Usage

Weight loss, antioxidant

Pregnancy Category

Information regarding safety and efficacy in pregnancy is lacking. Avoid use.

Dosing

- Since there are so many over-the-counter dietary supplements that contain bitter orange, consumers will need to rely on the manufacturers dosing instructions
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common

GI complaints (nausea), tachycardia, palpitation, increased blood pressure.

Adverse Reactions: Rare/Severe/Important

Cardiovascular collapse, arrhythmia, hypertensive crisis

Contraindications

Avoid in patients with hypertension, tachyarrhythmias, hyperthyroidism, narrow-angle glaucoma, pregnancy

Major Drug Interactions

Bitter Orange's Effect on Other Drugs

- Bitter orange has been shown to inhibit intestinal CYP3A4 and intestinal P-glycoprotein, and may interact with particularly moderate-to-strong substrates of these enzymes and transporter proteins
- Sympathomimetics: Increase toxicities (cardiovascular most significant)
- Anxiolytics and antidepressants: Increased serotonergic reactions (ranging from akathisia, myoclonic movements, tachycardia, up to hypertensive crisis and seizure)

Counseling Point

Carefully review ingredients that contain *Citrus aurantium* or bitter orange; since it is touted as a weight loss supplement, other herbal products that contain sympathomimetics or caffeine may be present and could be dangerous for patients with conditions such as uncontrolled hypertension or arrhythmias or taking drugs that interact with sympathomimetics/caffeine

Key Point

- Patients with uncontrolled hypertension, arrhythmias, hyperthyroidism, pregnancy, or narrow-angle–closure glaucoma should not take products that contain bitter orange
- "Ephedra free" does not mean sympathomimetic free. Bitter orange's main active ingredient is the sympathomimetic, synephrine.

BLACK COHOSH

Introduction

"Cohosh" comes from an Algonquian word meaning, "rough," and this widely found North American plant was used by Native Americans many centuries ago, mainly as a treatment for female reproductive problems. The "black" rhizome and root is the part of the plant that is used for its medicinal properties. The plant is also found worldwide and was also used in traditional Asian medicine and since the 17th century in Europe. The use of black cohosh today is for the management of symptoms during menopause in lieu of prescription hormone replacement therapy.

Mechanism of Action for the Drug Class

Some consider black cohosh to be a "phytoestrogen" (phyto = plant). The hormonal effects of black cohosh are believed to be the results of complex synergistic actions of

several "pre-estrogen" forming components. It is believed that black cohosh acts like a "SERM," that is, a selective estrogen receptor modulator.

Black Cohosh

Brand Names

Black cohosh is found as an ingredient in branded products, such as Remifemin, Estro Soy

Generic Names

Black cohosh, *Actaea racemosa*, baneberry, black snakeroot, bugbane, cimicifuga, rattle root, rattle top, squawroot

OTC

Dosage Forms

Tablet, capsule

Usage

Alleviation of symptoms of menopause ("hot flashes")

Pregnancy Category

Do not use in pregnancy; contraindicated.

Dosing

- 40–160 mg daily for perimenopausal symptoms
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common

Nausea, vomiting, vertigo

Adverse Reactions: Rare/Severe/Important

Case reports of hepatotoxicity

Contraindications

Should avoid in women with estrogen-positive breast cancer and pregnancy. Some formulations may contain salicylates and, therefore, should be avoided in patients with hypersensitivity to aspirin.

Major Drug Interactions

- Potential antagonism with anti-estrogenic therapy; and synergism (some beneficial/some harmful) with estrogen therapy
- Avoid use with known hepatotoxic drugs, as case reports have linked some serious hepatotoxicity (leading to liver transplant or death) with black cohosh use

Counseling Points

- Women considering the use of black cohosh to manage perimenopausal symptoms should consult with their physician or gynecologist prior to use to assess any risk of therapy with a phytoestrogen
- It may take 4 to 12 weeks of therapy with black cohosh to see full benefit for perimenopausal symptom relief
- Do not use if pregnant

Key Points

- Case reports of severe hepatotoxicity reported, some leading to transplant and death
- Avoid use in patients with liver disease or other drugs that are hepatotoxic

CAFFEINE

Introduction

Whether it is from coffee, black teas, cola products, energy drinks, or OTC supplements, everyone is aware of the "pick me up effects" of caffeine. Caffeine is sold as a supplement for energy, "staying alert," and in diet and exercise/bodybuilding supplement, generally as part of a multi-ingredient product. Natural sources of caffeine that can be incorporated into a supplement can be labeled as "kola nut," yerba mate, guarana, guayusa, and yaupon. This monograph will focus on caffeine primarily as an over-the-counter supplement to restore mental alertness or wakefulness, and being part of multi-ingredient supplements for weight loss and muscle building. Medical uses for caffeine, such as its use in respiratory depression, apnea of prematurity, relief of pain in spinal puncture headache, and others will not be discussed here.

Mechanism of Action for the Drug Class

Caffeine acts as a CNS stimulant, which increases wakefulness; it can also increase medullary respiratory center sensitivity to carbon dioxide and improve skeletal muscle contraction

Caffeine

Brand Names

NoDoz; NoDoz Maximum Strength, Vivarin, Stay Awake
Popular Energy Drink Brands: 5-Hour Energy, Full Throttle, Red Bull

Generic Names

Caffeine, kola nut, guarana, guayusa, yaupon, yerba mate

OTC

Dosage Forms
Tablet, capsule, energy drinks

Usage
Increased alertness, wakefulness

Pregnancy Category
Limit caffeine intake from all sources to ≤ 200 mg/day

Dosing
- For most adults, a caffeine intake of 400 mg is considered to be safe; some agencies recommend not exceeding an intake of 450 mg daily; as mentioned above, pregnant women should not exceed 200 mg of caffeine daily.
- Most OTC supplements do not focus on limiting intake with instructions, such as "100–200 mg every 3 to 4 hours as needed," which can expose consumers to adverse effects of caffeine.
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common
Flushing, palpitations, tachycardia, agitation, "jitters"/tremors, insomnia, irritability, diuresis, mood swings, tachypnea, hypertension

Adverse Reactions: Rare/Severe/Important
Seizure, ventricular arrhythmias, psychosis, delirium, hallucination, increased intraocular pressure

Contraindications
Should avoid in women with estrogen-positive breast cancer and pregnancy. Some formulations may contain salicylates and, therefore, should be avoided in patients with hypersensitivity to aspirin.

Major Drug Interactions
Caffeine is a major substrate of CYP1A2 and, to a lesser degree, a minor substrate of other CYP P450 enzymes.

Drugs Affecting Caffeine
- Ciprofloxacin and norfloxacin can increase the concentration of caffeine
- Sympathomimetics increase the stimulatory effects of caffeine
- Serotonergic agents and MAO-I should be used with caution
- Consumers should be aware of dietary supplements that contain sympathomimetics as either coingredients with caffeine or sole ingredients. These products, like caffeine, are used for weight loss, energy, and body building. Some examples are bitter orange, ephedra/ma huang, and Garcinia cambogia.
- Theophylline use with caffeine increases toxicities ranging from tremors, palpitations, up to serious effects, such as arrhythmias and seizures

Caffeine's Effect on Other Drugs
- Adenosine: Caffeine-containing products can diminish the effect of adenosine. This is especially important when adenosine is being used in a diagnostic procedure; avoid caffeine in advance of scheduled diagnostics using adenosine.

Counseling Points
- Limit supplementation; not to exceed, from all sources of caffeine, 400–450 mg daily, if tolerated
- Limit intake of caffeine from all sources to ≤ 200 mg daily if you are pregnant

Key Point
Be aware of multiple sources of caffeine, from dietary and common beverages, to over the counter supplements, to energy drinks

CHAMOMILE

Introduction
Chamomile is a popular herbal supplement most often associated with teas, but it has also been used and touted as a "calmative" and gastrointestinal antispasmodic. It is also used for skin inflammation and other indications. Clinical trials supporting any use of chamomile for medical conditions are very limited.

Mechanism of Action for the Drug Class
It is thought that the anti-inflammatory effects are related to several chemical constituents of chamomile, namely bisabolol and flavonoids, which have demonstrated antispasmodic effects in animals. Its use as a calmative in some animal models is attributed to apigenin, a chamomile extract that affects benzodiazepine binding sites in the brain.

◉ Chamomile

Brand Names
Generics only

Generic Names
Chamomile, *Matricaria recutita*, *Chamaemelu nobile*

OTC

Dosage Forms
Tablet, capsule, liquid extract, tea, topical cream

Usage
GI antispasmodic, calmative, anti-inflammatory

Pregnancy Category
Poorly documented adverse reactions have been reported (e.g., abortifacient effects, menstrual cycle irregularities, uterine stimulation with excessive use). Well-documented information regarding safety and efficacy in pregnancy is lacking. However, because it may possess weak estrogenic activity, avoid use in pregnancy.

Dosing
- Typical oral dose: 9–15 g daily
- See specific manufacturers' labels for other dosage forms (topicals, teas)
- Renal dosage adjustment: None

Adverse Reactions: Most Common
Patients who are sensitive to ragweed or who get hay fever have been known to "cross-react" when exposed to chamomile-containing products

Adverse Reactions: Rare/Severe/Important
None

Major Drug Interactions
Chamomile's Effect on Other Drugs

Warfarin: May increase effect (case reports of bleeding with warfarin)

Counseling Point
If you are allergic to ragweed or flowers, such as chrysanthemums and asters, avoid use of chamomile-containing products

Key Points
- Best to avoid during pregnancy and lactation due to purported estrogenic effects
- Gargles of chamomile flowers used as a natural treatment for chemotherapy-induced mucositis were no more effective than placebo in a clinical trial

CHONDROITIN

Introduction
Derived from animal cartilage, chondroitin is a popular and relatively safe natural supplement used to reduce the pain of osteoarthritis.

Mechanism of Action for the Drug Class
This mixture of polysulfated glycosaminoglycans (e.g., chondroitin-4-SO_4, chondroitin-6-SO_4) serves as a substrate for cartilage synthesis and may inhibit leukocyte elastase and improve joint mobility

◉ Chondroitin

Brand Names
Cosamin, Cosamin DS, Cosamin Protek, others

Generic Name
Chondroitin

OTC

Dosage Forms
Tablet, capsule, liquid extract

Usage
Pain relief from osteoarthritis, maintenance of joint cartilage

Pregnancy Category
Information regarding safety and efficacy in pregnancy is lacking. Avoid use.

Dosing
- 200–400 mg 2 to 3 times daily
- Maximum dose: 1200 mg daily
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common
Nausea, diarrhea, mild epigastric pain, headache

Adverse Reactions: Rare/Severe/Important
Myelosuppression (very rare)

Major Drug Interactions
Theoretic interaction with anticoagulants because chondroitin's structure is similar to heparinoid compounds

Counseling Points

- Animal sources of chondroitin (e.g., bovine, porcine, shark) may pose risk of transmitting infectious agents; use products from trusted manufacturers
- Often found in combination products with glucosamine, although frequently in amounts lower than label claims
- Multi-ingredient products containing manganese may provide doses of this mineral above the tolerable upper limit for adults (11 mg)

Key Point

Best to avoid during pregnancy and lactation until safety data are available

CINNAMON

Introduction

Best known as an aromatic and spice, cinnamon has been used in some cultures for GI disorders and as an antimicrobial, an antidiarrheal, and a dysmenorrheal. However, limited scientific data support these uses. In addition, claims have been made of cinnamon's antidiabetic properties, but data are also lacking to support this use.

Mechanism of Action for the Drug Class

Cinnamon bark and essential oils of cinnamon have been shown to have in vitro activity against some bacterial endotoxins, as well as fungal aflatoxins. Prostaglandin inhibition has been demonstrated with cinnamon, leading to its use as an anti-inflammatory. Polyphenols isolated from cinnamon have been shown to demonstrate some insulin-like activity.

◉ Cinnamon

Brand Name

Cinnulin PF

Generic Name

Cinnamon

OTC Dosage Forms

Tablet, capsule, ground cinnamon

Usage

Antimicrobial, antidiabetic agent, antioxidant

Pregnancy Category

Information regarding safety and efficacy in pregnancy is lacking. Generally recognized as safe when used in food.

Dosing

- Cinnulin: 250 mg twice daily before meals
- Ground powder: 1.0–1.5 g per day
- Renal dosage adjustment: None

Adverse Reactions: Most Common

None. The FDA gives cinnamon GRAS status (generally recognized as safe).

Adverse Reactions: Rare/Severe/Important

When cinnamon is ingested in large quantities in bark or oil form, increases in heart rate, breathing, GI motility, and perspiration have been noted

Major Drug Interactions

Theoretical synergistic effect with antidiabetic agents

Counseling Points

- Avoid ingestion of large quantities of bark or oil due to unwanted adverse effects
- Do not use as the sole agent to self-treat diabetes. Research has demonstrated no significant effect on cinnamon's ability to lower blood glucose or glycohemoglobin.

Key Points

- 500 mg of Cinnulin aqueous extract is equivalent to approximately 10 g of cinnamon powder
- If pregnant, avoid doses above those found in food, because safety and efficacy have not been proven

COCONUT OIL

Introduction

Sometimes referred to as the "tree of life," the coconut palm tree provides a vital food source, particularly in Asian and Indian culture. Coconut oil is widely used today in cosmetics and for cooking. In addition to being a food source, cultures have used coconut oil for conditions such as hair loss, burns, and heart problems. As with many "traditional medicines/treatments," the data on coconut oil ingestion to treat medical conditions is not substantiated in clinical trials. Excessive consumption of coconut oil can lead to dyslipidemia, as 90% of coconut oil is composed of saturated fats. Although used topically, for treatment of eczema, and to support healthy hair, dietary supplements by definition are ingested and will be highlighted in this monograph.

Mechanism of Action for the Drug Class

Coconut oil is composed mainly of saturated fats (90%), primarily lauric acid and other polyunsaturated and monounsaturated fatty acids. Long and medium chain triglycerides are also present. Coconut oil also contains vitamin E and minerals, such as phosphorous, zinc, and iron.

◉ Coconut Oil

Brand Names

None specific

Generic Names

Coconut oil, copra oil, palm oil

OTC

Dosage Forms

Capsule, oil/emulsion

Usage

Alzheimer's disease

Pregnancy Category

Information regarding safety and efficacy in pregnancy is lacking.

Dosing

- Not clearly studied for information on therapeutic dosing. 15 ml/day and gradual increases to 60–90 ml daily have been suggested in Alzheimer disease; however, clinical trials to substantiate this are lacking. Excessive consumption of coconut oil can contribute to dyslipidemia and potential cardiovascular disease.
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common

GI complaints (diarrhea, bloating, cramping)

Adverse Reactions: Rare/Severe/Important

Dyslipidemia in excessive consumption

Contraindications

No major contraindications noted

Major Drug Interactions

Information lacking

Counseling Points

- Excessive consumption can lead to dyslipidemia
- Topical application appears safe

Key Point

Best to avoid during pregnancy and lactation until safety data are available

CO-ENZYME Q

Introduction

Co-enzyme Q is a popular antioxidant that consumers use to promote "heart health."

Mechanism of Action for the Drug Class

Co-enzyme Q, a mitochondrial enzyme synthesized endogenously and containing 10 isoprenoid subunits, is involved in electron transport and ATP generation

◉ Co-enzyme Q

Brand Names

Heart Actives, Heart Support, Pure CoQ-10, Q-Gel, Q-Sorb, others

Generic Names

Co-enzyme Q, co-enzyme-Q_{10}, CoQ, CoQ_{10}, ubiquinone, ubidecarenone

OTC

Dosage Forms
Tablet, capsule, liquid extract

Usage
Antioxidant activity for several disorders, particularly cardiovascular disease (e.g., cardiomyopathy, heart failure, hypertension), HIV, and Parkinson's disease; prevention of statin-induced myopathy

Pregnancy Category
Information regarding safety and efficacy in pregnancy is lacking. Avoid use.

Dosing
- Usual dose: 50–200 mg daily
- Heart failure: 50 mg twice daily
- Hypertension: 60 mg twice daily
- Angina: 50 mg 3 times daily
- HIV: 200 mg daily
- Parkinson's disease: Up to 1200 mg daily
- Prevention of statin-induced myopathy: 150–250 mg daily
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common
Anorexia, nausea, vomiting

Adverse Reactions: Rare/Severe/Important
Headache, dizziness, fatigue, maculopapular rash, thrombocytopenia, elevated liver function tests, hypotension

Major Drug Interactions
Drugs Affecting Co-enzyme Q

HMG-CoA reductase inhibitors and beta blockers: Reduce serum concentration

Co-enzyme Q's Effect on Other Drugs

Warfarin: Decreases effect (theoretic only)

Counseling Points
- Use only with medical supervision for cardiovascular disorders
- Take with food

Key Points
- Supplied exogenously through many foods and also synthesized endogenously (sharing some synthetic pathways with cholesterol), but significance of source to co-enzyme Q status not yet clear
  - Data (from six clinical studies and one meta-analysis) show that co-enzyme Q has not been shown to be effective for prevention of statin-induced myopathy in double-blinded, randomized, controlled trials. Use for this indication is not advisable.
- Best to avoid during pregnancy and lactation until safety data are available

CRANBERRY

Introduction
The main reason that consumers seek out the use of cranberry supplements and even cranberry juice is the belief that cranberry may prevent recurrent urinary tract infections. There are some data to support this. Cranberry, though, is not to be used to treat urinary tract infections.

Mechanism of Action for the Drug Class
Cranberry's usefulness for the prevention of urinary tract infections is that it blocks the adhesion of pathogenic organisms, namely, *E. coli,* to cells of the urinary tract. Chemicals within cranberry, namely, proanthocyanidins, are potent inhibitors of bacterial adhesion. The adhesion of these bacteria to a tissue surface is one of bacteria's virulent factors to initiate many infectious diseases. Earlier hypotheses stated that cranberry's effect as a prophylaxis against urinary tract infections was an acidic pH change in the urine, however, the anti-adhesion properties are the most likely mechanism for its use with urinary tract issues.

Cranberry

Brand Names
Cranberry is found as an ingredient in branded products, such as Azo, Azo Urinary Tract Defense, Azo Cranberry, and many other products.

Generic Names
Cranberry, *Vaccinium macrocarpon,* Arandano Americano, Grosse moosbeere, Tsuru-kokemomo

OTC

Dosage Forms
Tablet, capsule, "gummies"

Usage
Prevention of urinary tract infections

Pregnancy Category

Information regarding safety and efficacy in pregnancy is lacking. If taken in moderation as cranberry juice or pure supplement, cranberry is considered to be relatively safe

Dosing

- Concentrated cranberry extract in the form of tablets, capsules, "gummies" range from 600–1200 mg daily
- Juice consumption, very often is in the form of "cocktails," where it may only contain up to 25% pure cranberry juice, have ranged from 120 ml up to a liter per day
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common

Excessive consumption of cranberry juice cocktail due to the sugar additives can lead to weight gain, exacerbation of diabetes, diarrhea, and other GI symptoms

Adverse Reactions: Rare/Severe/Important

Possible formation of calcium oxalate kidney stones; should avoid use in patients with nephrolithiasis

Contraindications

No major contraindications noted

Major Drug Interactions

- The composition of bioactive components of formulations of cranberry juice and supplements; it is not clear how it can affect drug metabolism and interactions
- However, one of the most "over-hyped" drug interactions with cranberry is with warfarin. Although case reports exist in the literature, none of these reports can explain a clear cut mechanism of the theorized interaction. Clinical pharmacokinetic studies have found no clinically relevant interactions between cranberry and warfarin.

Counseling Point

Cranberries contain oxalates and may form renal calculi (kidney stones). For patients prone to frequent kidney-stone formation, supplements and/or excessive consumption of cranberry juice should be avoided.

Key Point

If symptoms of urinary tract infections become more severe while on cranberry, other treatments may be required; seek medical attention

CREATINE

Introduction

Popular among younger consumers, creatine supplements are used to enhance muscle strength and athletic performance.

Mechanism of Action for the Drug Class

Synthesized endogenously and stored predominantly in skeletal muscle as creatine-phosphate. It serves as a high-energy phosphate source during anaerobic metabolism.

◉ Creatine

Brand Names

CRE Active, Creatine Blast, Creatine Fuel, Creatine Powder, CreaVATE, others

Generic Names

Creatine, creatine monohydrate, N-amidinosarcosine, N- (amino-imino-methyl)-N-methylglycine

OTC

Dosage Forms

Capsule, powder

Usage

Improves muscle strength, athletic performance, and recovery during exercise

Pregnancy Category

Information regarding safety and efficacy in pregnancy is lacking. Avoid use.

Dosing

- Initial or loading dose of 5 g 4 times daily for 2 to 5 days followed by 2–5 g daily for 1 to 5 weeks
- May be supplied in varying doses as an ingredient in different exercise or "body-building" supplements
- Renal dosage adjustment: Not known, but avoid use in renal dysfunction

Adverse Reactions: Most Common

Nausea, abdominal pain, diarrhea

Adverse Reactions: Rare/Severe/Important

Renal failure

Major Drug Interactions

Use with other drugs that may affect renal hemodynamics (NSAIDs, ACE inhibitors/angiotensin receptor blockers, and/or diuretics) can increase the risk of renal failure

Counseling Points

- Maintain adequate hydration (at least 2000 ml of water daily)
- Avoid use in combination with caffeine and ephedra
- Products may contain an impurity from processing (dicyandiamide)

Key Points

- Average diet supplies about 2 g creatine daily as well as the amino acid precursors for endogenous synthesis
- Best to avoid during pregnancy and lactation until safety data are available

NATURAL SUPPLEMENT, DHEA (DEHYDROEPIANDROSTERONE)

Introduction

Dehydroepiandrosterone, better known as DHEA, was once called the "fountain of youth" hormone, supplementing declines in androgen hormones as one ages. DHEA is a weak androgen and acts as a precursor in the production of sex hormones. DHEA and its metabolites are major circulating hormones in the body, peaking in early adulthood and declining to 10% to 20% between the ages of 70 and 80.

Mechanism of Action for the Drug Class

DHEA is produced endogenously in the adrenal gland from cholesterol but can also be synthesized in neurons and glial cells. It serves as a precursor to sex hormones.

◉ DHEA

Brand Names

In most products, DHEA is incorporated into the name of the product, with no well-known specific branded product. Also, it is incorporated into multi-ingredient products for muscle building, energy, libido-boosters, and "anti-aging" supplements.

Generic Names

Dehydroepiandrosterone, DHEA, Prasterone

OTC

Dosage Forms

Tablet, capsule, intraoral sprays, transdermal creams and gels.

Usage

"Anti-aging," muscle building, libido booster, perimenopausal symptoms

Pregnancy Category

Do not use in pregnancy; contraindicated.

Dosing

- 25–100 mg daily
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common

Acne, hirsutism, dyslipidemia (decreased HDL), hypertension, gynecomastia in men, oily skin, insomnia, mood changes

Adverse Reactions: Rare/Severe/Important

Case reports of hepatotoxicity

Contraindications

Should avoid in women with estrogen-positive breast cancer and pregnancy. Avoid in men with prostate cancer

Major Drug Interactions

Avoid use with known hepatotoxic drugs, as case reports have linked some serious hepatotoxicity (leading to liver transplant or death) with black cohosh use

Counseling Points

- Women considering the use of DHEA to manage perimenopausal symptoms should consult with their physician or gynecologist prior to use to assess any risk of therapy with a sex hormone precursor
- Do not use if pregnant
- Men with BPH should consult with a physician prior to using DHEA; contraindicated in prostate cancer
- DHEA may be contained in many multi-ingredient, body-building, and anti-aging supplements; read labels carefully

Key Points

- Case reports of severe hepatotoxicity reported, some leading to transplant and death; avoid use in patients with liver disease or other drugs that are hepatotoxic
- DHEA is prohibited under the World Anti-Doping Code and is screened for a chemical in athletic performance enhancers
- The FDA banned DHEA in 1985 as an OTC supplement for safety reasons, however, with the passage of the dietary supplement Health and Education Act of 1994 (DSHEA), nonprescription sales were allowed as a dietary supplement

ECHINACEA

Introduction

Echinacea is primarily used as an immune "booster" and is usually derived from the *Asteraceae* genus of plants. This genus includes the purple coneflower, which is the most common botanical source.

Mechanism of Action for the Drug Class

A number of polysaccharides, alkylamides, caffeic acid esters (echinacosides), and other constituents, which vary among species and plant parts, possess nonspecific immunomodulatory activity. It is thought that these constituents alter cell surface binding (T lymphocytes, macrophages) and increase cytokine production.

◉ Echinacea

Brand Names

EchinaGuard, Echinaforce, Esberitox, Echinacea, others

Generic Names

Echinacea, *Echinacea purpurea*, *Echinacea angustifolia*, *Echinacea pallida*, black-eyed susan, coneflower, hedgehog, Indian head, purple coneflower, snakeroot

OTC

Dosage Forms

Tablet, capsule, liquid extract

Usage

Immune system booster, treatment of the common cold, prevention and treatment of minor upper respiratory infections

Pregnancy Category

Information regarding safety and efficacy in pregnancy is lacking. Avoid use.

Dosing

- 900 mg 3 times daily of portions of *E. purpurea* standardized to 4% phenolics
- Because preparations vary, always refer to specific manufacturer's instructions for dosing
- 0.25–1.0 ml 3 times daily of a liquid extract (1:1 in 45% ethanol)
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common

GI complaints (altered taste, nausea, vomiting); neurologic complaints (transient tiredness, somnolence, dizziness, headache); dermatologic reactions (allergic skin reaction, eczema); asthma exacerbation; anaphylaxis

Adverse Reactions: Rare/Severe/Important

Hepatotoxicity with long-term chronic use and or use with other known hepatotoxins

Contraindications

Patients on immunosuppressant therapy should avoid use of echinacea because of a theoretic interaction with concurrent use. Patients with autoimmune disorders (e.g., rheumatoid arthritis, lupus) should avoid the use of this dietary supplement.

Major Drug Interactions

Echinacea's Effect on Other Drugs

- Immunomodulating agents: Potential interference with (theoretic)
- CYP3A4 or P-glycoprotein: May inhibit levels of CYP3A4 or P-glycoprotein substrates (low risk)

Counseling Points

- Limit continuous use to 2 to 8 weeks
- Value for treatment may exceed that for prevention of upper respiratory infections
- Avoid use if you have a history of allergy to ragweed, daisies, sunflowers, and/or chrysanthemums, because they are likely to cross-react with Echinacea

Key Points

- Contraindicated for patients with autoimmune diseases and/or on immunosuppressant agents
- Best to avoid during pregnancy and lactation until safety data are available

FEVERFEW

Introduction

Feverfew is one of the more commonly used herbal supplements because of its purported anti-inflammatory and analgesic effects. It is sometimes favored as a natural product for migraine sufferers.

Mechanism of Action for the Drug Class

Various metabolites, including parthenolide, inhibit prostaglandin synthesis, platelet aggregation, and leukotriene synthesis

◉ Feverfew

Brand Names

Feverfew Extract, Herbal Sure Feverfew, Mygrafew, NuVeg Feverfew Leaf, Premium Feverfew Leaf

Generic Names

Feverfew, *Tanacetum parthenium*

OTC

Dosage Forms

Tablet, capsule, liquid extract

Usage

Pain and inflammation; headache, including migraine treatment and prophylaxis

Pregnancy Category

Information regarding safety and efficacy in pregnancy is lacking. Avoid use. Based on the antiprostaglandin effect of this dietary supplement, fetal toxicity may be expected to be similar to what one may see with nonsteroidal anti-inflammatory drugs (NSAIDs), including premature closure of the ductus arteriosus and fetal nephro- and cardiotoxicity.

Dosing

- 200–250 mg daily
- Renal dosage adjustment: Not known; however, use with caution in patients with renal impairment due to expected effects on renal prostaglandins

Adverse Reactions: Most Common

Avoid skin contact due to high potential for sensitization, transient tachycardia, bruising, bleeding, GI ulceration, abdominal pain, diarrhea

Adverse Reactions: Rare/Severe/Important

Renal failure, hepatotoxicity

Contraindications

Based on the antiprostaglandin effect of feverfew, fetal toxicity can be expected; similar to what one may see with nonsteroidal anti-inflammatory drugs (NSAIDs), including premature closure of the ductus arteriosus and fetal nephro- and cardiotoxicity

Major Drug Interactions

Drugs Affecting Feverfew

- NSAIDs: Concurrent use can increase risk of GI toxicities (dyspepsia, GI ulceration) and nephrotoxicity

Feverfew's Effect on Other Drugs

- Antiplatelet agents and anticoagulants: May increase risk of bleeding
- Use caution with drugs that can negatively impact renal hemodynamics, such as diuretics, ACE inhibitors/angiotensin receptor blockers, NSAIDs, methotrexate, lithium

Counseling Points

- Monitor for signs and symptoms of bleeding, especially if using concurrent therapies, such as anticoagulants, NSAIDs, and antiplatelet therapy
- Discontinue 7 to 10 days before elective surgery
- Monitor for any changes in renal function, particularly if using concurrent NSAIDs, ACE inhibitors, angiotensin receptor blockers, and/or diuretics

Key Points

- Avoid in patients with severe renal disease
- Avoid during pregnancy, particularly during the third trimester, due to inhibition of prostaglandins on fetal cardiac physiology

FLAXSEED OIL

Introduction

Flaxseed oil contains various essential fatty acid but is particularly rich in alpha linoleic acid (ALA). Derived from the flaxseed, which, in various forms, has been part of the diet of people of Asia, Africa, and Europe; it also has a long history of being used as a medicinal "panacea." Today, it is most often used as a cardioprotectant, centering on preventing coronary artery disease.

Mechanism of Action for the Drug Class

The medical properties of flaxseed oil focus on the fatty acids that are contained within, mainly alpha linoleic acid. This polyunsaturated fat that comprises ~70% of flaxseed oil, is a rich source of omega-3 fatty acid. These fatty acids are critical for the integrity of cell membranes. It is suggested that the omega-3 alpha linoleic acid component in flaxseed oil contribute to the anti-atherogenic effect via anti-inflammatory and anti-proliferative mechanisms. Also, it is suggested that flaxseed oil may also protect against ischemic heart disease by improving vascular relaxation responses and inhibiting the incidence of ventricular arrhythmias.

◉ Flaxseed Oil

Brand Names

None in particular, the name flaxseed oil is generally incorporated into manufacturers' products

Generic Names

Flaxseed oil, linseed oil

OTC

Dosage Forms

Liquid, capsules

Usage

Cardioprotectant, Anti-inflammatory, diabetes, menopause, hyperlipidemia

Pregnancy Category

Information regarding safety and efficacy in pregnancy is lacking. Avoid use.

Dosing

- Dosing varies, but for reduced coronary artery disease and lipid lowering effect, doses up to 60 ml of flaxseed oil are used; some benefits are even seen with doses as low as 5 ml daily
- Renal dosage adjustment: None

Adverse Reactions: Most Common

GI complaints (diarrhea, bloating), allergy

Adverse Reactions: Rare/Severe/Important

Anaphylaxis

Contraindications

Avoid in patients with hypersensitivity to flax or flaxseed

Major Drug Interactions

Flaxseed Oil's Effect on Other Drugs

Enhanced effects if combined with laxatives based on the fiber content in flaxseed

Counseling Points

- A quality, cold-pressed flaxseed oil is a good source of alpha lineolic acid
- Flaxseed oil is not a sole adequate substitute for animal sources of omega-3 essential fatty acids. Vegans/vegetarians will be at risk for omega-3 fatty acid deficiency if they believe flaxseed oil will serve as an adequate substitute.

Key Point

Best to avoid during pregnancy and lactation until safety data are available

GARCINIA CAMBOGIA

Introduction

Garcinia, is a genus of evergreen fruit-bearing plants, and it is the species, *Garcinia cambogia*, that is being sold and used as a dietary supplement for weight loss. The fruit from this plant has been used for centuries in traditional Asian medicine, for uses ranging from flatulence, to inflammation, to an antibacterial.

Mechanism of Action for the Drug Class

Because supplements from the *Garcinia* genus are used for many conditions, the mechanism of action ranges from free radical scavenging acting as an antioxidant, and blocking key inflammatory proteins. It is believed that it works for weight loss through the key active component of *Garcinia cambogia*, which is hydroxycitric acid (HCA). HCA is believed to inhibit lipogenesis, increase lipid oxidation, and suppress appetite with reduction of food intake. HCA also competitively inhibits certain extra-mitochondrial enzymes that play a role in fatty acid biosynthesis.

◉ Garcinia cambogia

Brand Names

Garcinia cambogia is found as an ingredient in branded products such as Hydroxycut, Leptoprin, Xango, and scores of other products

Generic Names

Garcinia, *Garcinia cambogia, Garcinia indica,* garcinol, camboginol, Malabar tamarind

OTC

Dosage Forms

Tablet, capsule

Usage

Weight loss, anti-inflammatory, infection, hyperlipidemia, diabetes, GI disorders (flatulence, dyspepsia)

Pregnancy Category

Information regarding safety and efficacy in pregnancy is lacking. Avoid use.

Dosing

- Since there are so many OTC/dietary supplements that contain *Garcinia cambogia*, consumers will need to rely on the manufacturers dosing instructions. However, some references state that the maximum dose of *Garcinia cambogia* should be limited to 1500 mg/day.
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common

GI complaints (nausea, vomiting), dry mouth, dizziness, headache

Adverse Reactions: Rare/Severe/Important

Hepatotoxicity has been reported in some multi-ingredient products, and it is not certain if it is due to *Garcinia cambogia*, or other ingredients. Case reports of seizures, rhabdomyolysis, atrial fibrillation, renal failure have also been reported with multi-ingredient products that also contain *Garcinia cambogia*.

Contraindications

No major contraindications noted

Major Drug Interactions

Garcinia Cambogia's Effect on Other Drugs

- *Garcinia cambogia* contains iron and thus may have additive adverse effects for patients using iron supplements
- Potential additive effects to lower blood glucose with other drugs used to treat diabetes

Counseling Point

Carefully review ingredients that contain *Garcinia cambogia*, since it is touted as a weight loss supplement; other herbal products that contain sympathomimetics or caffeine may be present; and could be dangerous for patients with conditions such as uncontrolled hypertension, arrhythmias, or taking drugs that interact with sympathomimetics/caffeine

Key Point

Best to avoid during pregnancy and lactation until safety data are available

GARLIC

Introduction

Garlic, a popular botanical, is believed to have many pharmacologic effects, leading to its use as an antiseptic, anti-hypertensive, antilipemic, and expectorant. It is thought that most of garlic's benefits are derived from the raw garlic clove vs commercially prepared products.

Mechanism of Action for the Drug Class

Alliins are the most active substances in garlic. It is thought that garlic alliins block adenosine triphosphate citrate lyases, an important enzymatic step in the process of converting carbohydrates to fat. Another substance in garlic, ajoene, seems to demonstrate antimicrobial properties. It is believed; however, that any pharmacologic effect with garlic is seen with the use of freshly prepared products vs commercialized capsules, tablets, and powders.

◉ Garlic

Brand Names

Garlicin, Garlique, Garlic Oil, Triple Garlic, Kyolic-Branded Products, High Allicin Garlic, Odor-Free Concentrated Garlic

Generic Names

Garlic, *Allium sativum*, allium, clove garlic

OTC

Dosage Forms

Tablet, capsule, liquid extract, dried powder, raw garlic clove

Usage

Treatment of hyperlipidemia; treatment of high blood pressure; antiseptic agent

Pregnancy Category

Information regarding safety and efficacy in pregnancy is lacking. Avoid use.

Dosing

- Hyperlipidemia: Total daily dose of 600–900 mg of garlic powder (standardized to 1.3% of alliin content)
- Hypertension: 200–300 mg 3 times daily
- Antiseptic: Fresh garlic can be applied to the skin as an antimicrobial dressing for a few hours; prolonged contact may lead to skin irritation/burns
- Renal dosage adjustment: Not known

Essential Monitoring Parameter

Due to potential antiplatelet effects, monitor for any marked bruising or bleeding, particularly in patients taking drugs that increase bleeding risk

Adverse Reactions: Most Common

Headache, fatigue, myalgias, skin reactions/burns with prolonged application of fresh garlic preparations to skin, dyspepsia, body odor, halitosis, lacrimation

Adverse Reactions: Rare/Severe/Important

Increases bleeding risk, particularly when combined with antiplatelet agents and/or anticoagulants

Major Drug Interactions

Garlic's Effects on Other Drugs

Antiplatelets, NSAIDs, warfarin, anticoagulants: Increases bleeding risk

Counseling Points

- Increased bleeding risk when used with antiplatelets, NSAIDs, warfarin, and anticoagulants; monitor accordingly
- Discontinue 7 to 10 days before elective surgery
- Best therapeutic results are seen with freshly prepared garlic

Key Points

- Increased bleeding risk when used with antiplatelets, NSAIDs, warfarin, and anticoagulants; monitor accordingly
- Avoid use during pregnancy and lactation

GINGER

Introduction

The folk remedy of drinking ginger ale for nausea seems to have some validity. More recent interest in ginger centers on its use to prevent and manage nausea due to a variety of causes. Some other uses for ginger, mainly for arthritic pain, have been explored, but the data are insufficient to support this use.

Mechanism of Action for the Drug Class

Ginger's antiemetic properties are believed to be related to both enhanced GI transport and its anti-5-hydroxytryptamine effects

◉ Ginger

Brand Name

Generics only

Generic Names

Ginger, ginger root, *Zingiberis rhizoma*

OTC

Dosage Forms

Tablet, capsule, liquid extract

Usage

Treatment and management of nausea, motion sickness, chemotherapy-related nausea, postoperative nausea, pregnancy-related nausea

Pregnancy Category

Although studied for pregnancy-related nausea (morning sickness), the trials provided no data on fetal outcomes. Without these data, reasons for caution exist.

Dosing

- Nausea: 250 mg to 1 g; repeat 3 to 4 times daily
- Motion sickness: 250 mg to 2 g per dose; repeat 3 to 4 times daily
- Postoperative nausea: 1 g dose
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common

Heartburn, diarrhea, mouth irritation

Adverse Reactions: Rare/Severe/Important

Case report of arrhythmia

Major Drug Interactions

The interaction reported with warfarin may be "overhyped" due to the fact that pharmacokinetic studies demonstrated that warfarin kinetics were unchanged when co-administered with ginger, with no changes in protein binding or INR. Extra monitoring may be advised only in patients with high ginger intake.

Counseling Point

If nausea persists after several days with self-treatment with ginger, contact your healthcare provider

Key Point

Best to avoid during pregnancy and lactation until safety data are available

GINKGO BILOBA

Introduction

Supplements derived from *Ginkgo biloba* are used by those who believe it can improve memory and cognitive function.

Mechanism of Action for the Drug Class

The leaf extract contains terpene lactones (ginkgolides, bilobalide), flavonoids, and amino acids that contribute to antiplatelet, vasodilatory, and free-radical scavenging activity to improve circulatory flow. Ginkgolide B inhibits platelet-activating factors.

◉ Ginkgo

Brand Names

Ginkai, Ginkgold, Ginkgo

Generic Names

Ginkgo, *Ginkgo biloba*, bai guo ye, fossil tree, kew tree, maidenhair tree, salisburia

OTC

Dosage Forms

Tablet, capsule, tincture

Usage

Memory enhancer, cerebrovascular insufficiency (dementia, memory impairment), vertigo, tinnitus, peripheral vascular disease (intermittent claudication)

Pregnancy Category

Information regarding safety and efficacy in pregnancy is lacking. Avoid use.

Dosing

- 40–80 mg 3 times daily of a leaf extract standardized to 22% to 27% flavone glycosides and 5 to 7% terpenes
- Refer product labeling for dosing recommendations
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common

Nausea, vomiting, diarrhea, headache, dizziness, restlessness, palpitations, bleeding

Adverse Reactions: Rare/Severe/Important

Allergic skin reaction, Stevens-Johnson syndrome

Major Drug Interactions

Ginkgo's Effect on Other Drugs

- Antiplatelets and anticoagulants: Increases effects
- Antiepileptics: Decreases effects if excessive amounts of natural contaminant from ginkgo seeds are present

Counseling Points

- May require at least 4 weeks and possibly 6 to 8 weeks of treatment for full effect
- Report any skin rashes, unusual bruising, or bleeding to your healthcare provider
- Use caution if combined with other products that may possess antiplatelet or anticoagulant effects
- Discontinue 2 weeks before surgery to reduce bleeding risk
- May be taken without regard to meals or food intake

Key Points

- Avoid during pregnancy and lactation
- Increases the effect of antiplatelets and anticoagulants

GINSENG

Introduction

Ginseng (*Panax* spp.) is a very popular natural supplement worldwide. It is used as a general tonic to improve well-being and increase energy levels.

Mechanism of Action for the Drug Class

The mature root contains numerous triterpenoid saponins (ginsenosides) of varying composition and concentration between species, as well as flavonoids and vitamins, which may contribute to CNS stimulation/suppression, hypertension/hypotension, immunomodulation, and antioxidant and anti-inflammatory activities. These effects may occur through an effect on the hypothalamic-pituitary-adrenal (HPA) axis and neurotransmitter pathways.

◉ Ginseng

Brand Names

Ginsana, G-115, Ginseng

Generic Names

Ginseng, Asian ginseng (*Panax ginseng*), Chinese ginseng, Japanese ginseng, Korean ginseng, jintsan, red ginseng, ninjin, ren shen, seng, American ginseng (*Panax quinquefolius*), anchi ginseng, red berry, ren shen, sang, tienchi ginseng

OTC

Dosage Forms

Tablet, capsule, tincture

Usage

Improved well-being, energy boost, stress relief

Pregnancy Category

Information regarding safety and efficacy in pregnancy is lacking. Avoid use.

Dosing

- 200–600 mg daily of root extract standardized to 4% to 5% ginsenoside
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common

Headache, transient nervousness, insomnia, cerebral arteritis, mydriasis, disturbance of accommodation, hypertension, hypotension, hypoglycemia

Adverse Reactions: Rare/Severe/Important

Dermatologic reactions such as Stevens-Johnson syndrome, postmenopausal vaginal bleeding, breast tenderness

Major Drug Interactions

Ginseng's Effect on Other Drugs

- Warfarin: May decrease anticoagulant effect
- Antiplatelet agents: May increase bleeding risk
- Caffeine and products that contain natural guarana: May increase effects
- Monoamine oxidase inhibitors (MAOIs): May increase stimulant effect

Counseling Points

- Avoid doses > 3 g daily
- Take within 2 hours of a meal to avoid potential hypoglycemia
- Limit continuous use to < 3 months
- Siberian ginseng (*Eleutherococcus senticosus*) contains no ginsenosides and is actually a different botanical product called eleuthera

Key Point

Avoid use during pregnancy and lactation

GLUCOSAMINE

Introduction

Glucosamine, a very popular supplement for joint health, is used alone or in conjunction with chondroitin. Studies have shown mixed results on the benefits of glucosamine; however, it remains a favorite of consumers and has a relatively good safety record.

Mechanism of Action for the Drug Class

This hexosamine sugar is a substrate for glycoproteins, glycolipids, glycosaminoglycans, proteoglycans, and hyaluronic acid, all of which are required for cartilage synthesis

◉ Glucosamine

Brand Names

Cosamin, Cosamin DS, Cosamin Protek, others

Generic Name

Glucosamine

OTC

Dosage Forms

Tablet, capsule, liquid extract

Usage

Pain relief from osteoarthritis, maintenance of joint function

Pregnancy Category

Information regarding safety and efficacy in pregnancy is lacking. Avoid use.

Dosing

- 500 mg orally 3 times daily
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common

Altered taste, nausea, vomiting, constipation, flatulence, abdominal bloating, cramps, diarrhea, headache, allergic reactions (may cross-react in patients with severe shellfish allergies)

Adverse Reactions: Rare/Severe/Important

None reported

Contraindication

Patients with severe shellfish allergy should avoid using glucosamine. Although derived from the shells of these animals, some glucosamine products may contain shellfish protein, which could lead to an allergic reaction.

Major Drug Interactions

Glucosamine's Effects on Other Drugs

Insulin and oral antidiabetic agents: May decrease sensitivity to these agents. This is of primary concern in patients with hard to manage glycemic control (i.e., those with "brittle diabetes").

Counseling Point

Those with shellfish allergies should select products carefully because some formulations are derived from marine exoskeletons

Key Points

- Glucosamine sulfate has been studied more frequently than other salts
- Multi-ingredient products containing manganese may provide doses of this mineral above the tolerable upper limit for adults (11 mg)

GOLDENSEAL

Introduction

Goldenseal (*Hydrastis canadensis*) is native to the eastern United States. American Indians used goldenseal root as a stimulant, a diuretic, and even as an insect repellant. Today, people claim the usefulness of goldenseal in cold and flu preparations and eyewashes and as a treatment for topical infections and diarrhea.

Mechanism of Action for the Drug Class

Alkaloids of goldenseal have shown modest antimicrobial activity in vitro. In addition, it may also have a sodium-sparing diuretic effect, as well as immunostimulatory properties; however, the mechanism has not been well described.

◉ Goldenseal

Brand Names

Many different brands are available

Generic Names

Goldenseal, *Hydrastis canadensis*, yellowroot, orangeroot, eyeroot, goldenroot, jaundice root, yellow puccoon, Indian tumeric, sceau d'or

OTC

Dosage Forms

Tablet, capsule, liquid extract

Usage

Antimicrobial, antidiarrheal, diuretic, eye ailments

Pregnancy Category

Do not use during pregnancy. Goldenseal is a known uterine stimulant.

Dosing

- Varies considerably from 250 mg to 1 g 3 times daily, some labeling suggests doses as high as 3420 mg daily
- Extracts used for cold and influenza: 10 to 30 drops of the extract 2 to 4 times daily
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common

Anorexia, nausea, vomiting

Adverse Reactions: Rare/Severe/Important

Photosensitivity; very high doses may induce vomiting, nausea, anxiety, and/or seizures

Major Drug Interactions

Use with caution with cardiovascular agents because goldenseal causes vasodilation and hypotension

Counseling Points

- Use of high doses or doses not consistent with labeling increases the risk for serious adverse effects
- Use caution when self-treating eye ailments with goldenseal. It is better to seek medical attention from a specialist.

Key Points

- Goldenseal is a known uterine stimulant. Do not use during pregnancy.
- Although goldenseal has been touted as an "eye tonic" and eyewash, reports of ophthalmic phototoxicity with lens damage have been reported

KAVA

Introduction

Kava, or kava-kava, is a popular botanical derived from *Piper methysticum,* which is used for anxiety relief. However, it is a potentially dangerous herbal supplement. Warnings from the FDA have highlighted hepatotoxicity from this product. The sale of kava is banned in the United Kingdom, Germany, Switzerland, France, Canada, and Australia due to the risk of liver damage.

Mechanism of Action for the Drug Class

Kava lactones/pyrones have muscle-relaxing, anticonvulsive, and antispasmodic effects. Kava also has hypnotic, analgesic, and psychotropic properties. It can also inhibit cyclo-oxygenase 2.

◉ Kava

Brand Names

Pharma Kava, Kava Kava Premium

Generic Names

Kava, *Piper methysticum*, kava-kava, ava, ava pepper, intoxicating pepper, tonga, kew

OTC

Dosage Forms

Capsule, tincture, tea

Usage

Anxiety, stress, tension, agitation

Pregnancy Category

Information regarding safety and efficacy in pregnancy is lacking. Avoid use.

Dosing

- Capsules of kava root extract: 150–300 mg twice daily
- Tincture: Thirty drops with water 3 times daily
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common

CNS complaints of dizziness, headache, pupillary dilation

Adverse Reactions: Rare/Severe/Important

Case reports of hepatotoxicity, with some being irreversible and fatal. Kava dermopathy is a reversible darkening or yellowing of the skin with whitish scaly flakes.

Major Drug Interactions

Kava's Effect on Other Drugs

- Antiplatelets, NSAIDs, and anticoagulants: Increases bleeding risk; monitor accordingly
- Drugs metabolized by CYP1A2, 2C9, 2C19, 3A4: In vitro inhibition; exercise caution with concomitant use
- Centrally acting agents (benzodiazepines, barbiturates, opiates, ethanol): Increases CNS toxicities
- Dopaminergic agents (levodopa): Decreases effectiveness

Contraindications

Concurrent use of hepatotoxins or MAOIs

Counseling Points

- Increased bleeding risks when used with antiplatelets, NSAIDs, and anticoagulants; monitor accordingly
- Discontinue 7 to 10 days before elective surgery
- Avoid use with concurrent hepatotoxins; monitor for signs and symptoms of liver toxicity
- Food enhances absorption
- Notify your physician and pharmacist if self-initiating due to numerous drug interactions
- This product should be avoided because of the risk of liver toxicity

Key Points

- Avoid during pregnancy and lactation
- Avoid use with concurrent hepatotoxins; monitor for signs and symptoms of liver toxicity. Note FDA warning concerning kava.

MELATONIN

Introduction

Melatonin is noted for its effects on the sleep cycle and use as a sleep aid. Consumers who travel use melatonin to help allay feelings of tiredness from jet lag.

Mechanism of Action for the Drug Class

This pineal gland hormone is involved in regulating several functions, including the sleep–wake cycle (circadian rhythm). Melatonin is synthesized endogenously from serotonin.

◉ Melatonin

Brand Names
Melatonex, Melatonin, Melatonin Forte, Melatonin PM Complex

Generic Names
Melatonin, N-acetyl-5-methoxytryptamine

OTC

Dosage Forms
Tablet, capsule

Usage
Promotion of sleep, prevention of symptoms of jet lag, treatment of insomnia

Pregnancy Category
Information regarding safety and efficacy in pregnancy is lacking. Avoid use.

Dosing
- Sleep aid: 0.3–3 mg at bedtime
- Jet lag: Up to 5 mg daily for 3 days before and 3 days after air travel
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common
Neurologic complaints, including migraines, daytime drowsiness, and depression

Adverse Reactions: Rare/Severe/Important
Hypothermia, hypertension, retinopathy, seizure, infertility

Major Drug Interactions
Potentially additive effects with CNS depressants (e.g., narcotics, benzodiazepines)

Counseling Points
- Do not drive or operate machinery or engage in other skilled activities for several hours after taking melatonin
- Use only for short durations; do not use chronically
- Select immediate- over sustained-release products
- Select products containing synthetic melatonin over those derived from animal pineal glands

Key Point
Avoid during pregnancy, with breastfeeding, or if trying to conceive

MILK THISTLE

Introduction
Milk thistle is best known as a "liver tonic" due to its purported hepatoprotective effects. It has been used for centuries in the treatment of hepatobiliary disease.

Mechanism of Action for the Drug Class
The main active constituent of milk thistle, silymarin, inhibits the peroxidation of lipids within hepatic cells. The other active constituent, silibinin, decreases synthesis of cholesterol in the liver. In addition, silymarin may inhibit inflammatory and cytotoxic mediators. Both silymarin and silibinin are known to be free-radical scavengers, hence their antioxidant activity.

◉ Milk Thistle

Brand Names
Generics only

Generic Names
Milk thistle, holy thistle, lady's thistle, marian thistle, Mary thistle, St. Mary thistle, silybum

OTC

Dosage Forms
Tablet, capsule, liquid extract, crude milk thistle seed

Usage
Hepatoprotectant for hepatitis, cirrhosis, and other liver diseases; treatment of toxicity due to *Amanita mushroom* poisoning

Pregnancy Category
Information regarding safety and efficacy in pregnancy is lacking. Avoid use.

Dosing
- 420–600 mg daily in 2 divided doses
- Crude milk thistle seed has been used at 12–15 g per day for hepatitis and other liver conditions
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common
Anorexia, nausea, vomiting, bloating

Adverse Reactions: Rare/Severe/Important

None reported

Major Drug Interactions

- Inactivates CYP3A4 and 2C9. Clinical significance of this is not well defined. Use caution when using high-dose milk thistle with substrates of these enzymes with narrow therapeutic indices.
- Potent selective inhibitor of the enzyme UGT1A1. Clinical importance of this interaction is unknown.

Counseling Point

Do not self-treat liver conditions with milk thistle without proper diagnosis and medical management

Key Point

Best to avoid during pregnancy and lactation until safety data are available

PROBIOTICS

Introduction

Lactobacillus acidophilus is a normal gut flora bacterium and is one of the most commonly used probiotics. According to the World Health Organization (WHO), a *probiotic* is a supplement that contains live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. In addition to *L. acidophilus*, *Bifidobacterium bifidum,* and *Saccharomyces* derived from yeast also are found in probiotic supplements as well as yogurt. Sufficient clinical trials have been conducted to enable meta-analyses to be conducted for several clinical conditions. Evidence exists to support the use of probiotics in the treatment of bacterial vaginosis, diarrhea (acute infectious, antibiotic associated, and persistent), irritable bowel syndrome (IBS), necrotizing enterocolitis in neonates, and ventilator-associated pneumonia. Meta-analyses have shown no effect of probiotics on Crohn's disease, eczema, pancreatitis, or ulcerative colitis or in patients in intensive care.

Mechanism of Action for the Drug Class

Live gut microorganisms that, when ingested in food products or supplements, help to maintain or reestablish the normal bowel or vaginal flora

◉ Probiotics

Brand Names

These products may contain one or more of the previously mentioned bacteria; consult product-specific labeling for details: Align, Bacid Caplets, Bulgaricum IB, DDS-Acidophilus, Florajen, Acidophilus Extra Strength, Intestinex, Kyo-Dophilus, Lactinex, Lactinex Granules, Probiata, Probiotic Restore, Superdophilus

OTC

Dosage Forms

Capsule, powder, tablet

Usage

Treatment of uncomplicated diarrhea, particularly that caused by modification of intestinal flora by antibiotic therapy; diarrhea due to infections; ulcerative colitis; patients with colostomies with diarrhea or constipation; spastic diarrhea; bacterial vaginosis

Pregnancy Category

No adequate and well-controlled studies have been conducted in pregnant women. Pregnant women should only use *L. acidophilus* under medical supervision.

Dosing

Products vary from manufacturer to manufacturer and among batches produced by one manufacturer. Because it is often not clear what the product's active component(s) is, standardization may not be possible, making it difficult to compare the clinical effects of different brands. Dosing varies based on the particular product and dosage form. See individual product labels/instructions for dosing.

Adverse Reactions: Most Common

Flatulence with initial use

Adverse Reactions: Rare/Severe/Important

Case reports of fatal *Lactobacillus* septicemia in markedly immunocompromised patients who have used acidophilus/probiotic products

Contraindication

Patients with severe lactose intolerance/allergy should not use probiotics containing *L. acidophilus*

Major Drug Interactions

Antibiotics: Although often prescribed together with antibiotics to help prevent antibiotic-related diarrhea, these same antibiotics can be bacteriocidal to the *Lactobacillus,* rendering the probiotic ineffective. Probiotics are best used when a course of antibiotic therapy is completed.

Counseling Points

- Expect an increase in flatulence with initiation of probiotics
- It is best to wait to start to use probiotics until after the course of antibiotics has been completed
- When self-treating diarrhea with probiotics, seek out medical attention if there is no clear-cut benefit after 2 days of therapy or if fever develops

Key Point

Patients who are immunocompromised or taking immunosuppressant therapy should avoid the use of *L. acidophilus* and other probiotics

RED YEAST RICE

Introduction

Red yeast rice, which is derived from *Monascus purpureus*, is the natural source of mevinolin, the active ingredient in lovastatin. Its primary use is as a natural supplement to treat hyperlipidemia.

Mechanism of Action for the Drug Class

Red yeast rice forms naturally occurring HMG-CoA reductase inhibitors. The major active ingredient is monacolin K, which is also known as mevinolin/lovastatin. Inhibition of this enzyme is the rate-limiting step in the production of cholesterol.

Red Yeast Rice

Brand Name

Cholestin

Generic Names

Red yeast rice, *Monascus purpureus,* monascus, red mold, red rice yeast, rotschimmelreis (Europe); zhitai, hon-chi, xuezhikang (China); red-koji, beni-koji (Japan)

OTC

Dosage Forms

Capsule

Usage

Treatment of high cholesterol

Pregnancy Category

Contraindicated in pregnancy because it is a form of lovastatin. Prescription lovastatin is a Category X drug. Do not use red yeast rice if pregnant or planning to become pregnant.

Dosing

- 1200 mg twice daily
- Renal dosage adjustment: None

Adverse Reactions: Most Common

Nausea, anorexia, diarrhea

Adverse Reactions: Rare/Severe/Important

Myopathies and rhabdomyolysis, increased liver function tests

Major Drug Interactions

Drugs Affecting Red Yeast Rice

- Cyclosporine: Increases serum concentrations. Case reports have documented rhabdomyolysis with concomitant use.
- Grapefruit juice: Increases blood levels of the active ingredients in red yeast rice, leading to greater adverse reactions and potential liver damage
- CYP3A4 inhibitors: Theoretically will increase the active lovastatin-like ingredient in red yeast rice

Red Yeast Rice's Effect on Other Drugs

- Statins: Do not use with prescription statins. Concomitant use can lead to serious adverse reactions, including myopathies/rhabdomyolysis and hepatotoxicity.

Counseling Points

- Avoid self-treatment of lipid disorders without first being properly diagnosed by a healthcare provider
- Report any signs or symptoms to your healthcare provider of unexplained muscle aches, dark or tea-colored urine, yellowing of the skin/sclera, changes in urine output, or unexplained abdominal pain
- Use only with medical supervision for proper diagnosis of cardiovascular and lipid disorders
- Take with food

Key Points

- Contraindicated in women who are pregnant or planning to become pregnant
- Do not use red yeast rice with prescription statins

SAW PALMETTO

Introduction

Saw palmetto (*Serenoa repens* and *S. serrulata*) is touted for prostate health, although recent randomized, prospective, controlled trials have shown little benefit for this indication. Nonetheless, it remains a popular product among consumers.

Mechanism of Action for the Drug Class

The lipid fraction (fatty acids, sterols) in saw palmetto inhibits 5-alpha-reductase activity and possesses antiandrogenic, antiproliferative, and anti-inflammatory properties

◉ Saw Palmetto

Brand Names

Nutrilite, PROST Active, PROST Active Plus, Sabal Select, Solaray

Generic Names

Saw palmetto, *Serenoa repens*, *Serenoa serrulata*, American dwarf palm tree, cabbage palm, sabal fructus

OTC

Dosage Forms

Tablet, capsule

Usage

Symptoms of benign prostatic hypertrophy (BPH)

Pregnancy Category

Information regarding safety and efficacy in pregnancy is lacking. Avoid use.

Dosing

- 160 mg twice daily *or* 320 mg daily of a liposterolic extract of ripe fruit, standardized to 85% to 95% fatty acids/sterols
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common

Nausea, vomiting, constipation, diarrhea, headache, insomnia, dizziness, estrogenic effects (primarily manifested as breast tenderness and gynecomastia in men, decreased libido)

Adverse Reactions: Rare/Severe/Important

None

Major Drug Interactions

None

Counseling Points

- Before use, see healthcare provider to rule out prostate cancer
- May require at least 4 to 6 weeks and as long as 3 to 6 months for full effect, although the benefit is questionable

Key Points

- Avoid during pregnancy and lactation; not intended for women
- Does not seem to alter prostate size; questionable benefit, as demonstrated by randomized, prospective, controlled trials

ST. JOHN'S WORT

Introduction

St. John's wort (*Hypericum perforatum*) is widely touted for depression and is quite popular in Europe as well as in the United States and Canada for this indication. Clinical trials have demonstrated its effectiveness as an antidepressant for mild depression.

Mechanism of Action for the Drug Class

Extract from the flower contains naphthodianthrones (hypericins), flavonoids (hyperoside), phloroglucinols (hyperforin), and other constituents that probably have an inhibitory action on central serotonin, norepinephrine, dopamine, and gamma-aminobutyric acid reuptake.

◉ St. John's Wort

Brand Names

St. John's Wort (from various manufacturers)

Generic Names

St. John's wort, *Hypericum perforatum*, goat weed, hypericum, John's wort, Klamath weed, millepertuis, tipton weed

OTC

Dosage Forms
Tablet, capsule, liquid

Usage
Mild-to-moderate depression

Dosing
- 300 mg 3 times daily or 450 mg twice daily of a flower extract standardized to 0.3% dianthrones (or total hypericins) or 2% to 6% hyperforin
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common
Dry mouth, nausea, vomiting, constipation, abdominal pain, bloating, diarrhea, headache, dizziness, insomnia, fatigue, restlessness, anxiety, hypomania, serotonin syndrome, allergic skin reaction, photosensitivity, anorgasmia

Adverse Reactions: Rare/Severe/Important
Serotonin syndrome, hypertensive crisis

Major Drug Interactions
St. John's Wort's Effects on Other Drugs
- Benzodiazepines, cyclosporine, digoxin, estrogens/oral contraceptives, irinotecan, protease inhibitors, simvastatin, tacrolimus, theophylline, warfarin: Increases clearance because it is a strong enzyme inducer (CYP3A4, CYP2D6, CYP1A2, P-glycoprotein) through pregnane X receptor binding
- Antidepressants: Additive effects
- Serotoninergic-acting drugs (e.g., antidepressants, tramadol, meperidine, "triptans" for migraines): Additive effects
- Drugs known to be photosensitizers (i.e., amiodarone, methotrexate, tetracyclines): Increases phototoxicity

Counseling Points
- Requires at least 2 to 3 weeks of treatment for effect
- Take in the morning if you experience insomnia
- Limit sun exposure or use sunscreen
- Avoid alcohol
- Do not use with prescription antidepressants without the approval of a medical psychiatric professional

Key Points
- Avoid use during pregnancy and lactation
- Review any medications (prescription and nonprescription) the patient is taking because St. John's wort has numerous drug interactions
- Concomitant use with protease inhibitors or oral contraceptives is not recommended

VALERIAN

Introduction
Valerian (*Valeriana officinalis*) in the form of teas and capsules is used as a sleep aid. However, these same sedative effects can pose a risk to those using other CNS depressants.

Mechanism of Action for the Drug Class
Valerianic acid components have been shown to decrease the degradation of gamma-aminobutyric acid (GABA) with an increase of GABA at the synaptic cleft via inhibition of reuptake and an increase in secretion. This increase of available GABA may be one factor responsible for the sedative effects of valerian.

◉ Valerian

Brand Names
Herbal Sure Valerian Root, NuVeg Valerian Root, Quanterra Sleep, Natural Herbal Valerian Root, Nature's Root Nighttime

Generic Names
Valerian, *Valeriana officinalis*, valerian root, capon's tail, heliotrope, vandal root

OTC

Dosage Forms
Tea/teabag, extract, tablet, capsule

Usage
Sleep aid, insomnia caused by anxiety, restlessness

Pregnancy Category
Information regarding safety and efficacy in pregnancy is lacking. Avoid use.

Dosing
- Restlessness: 220 mg of extract 3 times daily
- Sleep aid: 400–900 mg 30 minutes before bedtime
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common
Nausea, vomiting, constipation, diarrhea, headache, insomnia, dizziness

Adverse Reactions: Rare/Severe/Important
Reports of hepatotoxicity (rare)

Major Drug Interactions

Valerian's Effects on Other Drugs

- Antiplatelet agents and anticoagulants: Increases risk of bleeding
- Barbiturates, benzodiazepines, ethanol, opiates: Increases CNS depression
- Hepatotoxins: May elevate transaminases; use with caution
- Iron: Binds with oral iron salts, leading to malabsorption; separate administration time by 1 to 2 hours
- Loperamide: Paradoxical delirium and confusion

Counseling Points

- Avoid driving or working with heavy equipment when starting therapy due to sedative effects
- Avoid use with alcohol or other sedatives
- Monitor for signs and symptoms of hepatotoxicity (dark amber urine, skin or eye jaundice/yellowing, right upper quadrant abdominal pain)

Key Point

Avoid use during pregnancy and lactation

NUTRIENTS AND VITAMINS

Introduction

Vitamins are macronutrients that are essential for life. They regulate metabolism and assist in different biochemical processes, such as the formation of hormones, blood cells, nervous system chemicals, and genetic material. They differ in their physiologic actions. The fat-soluble vitamins include vitamins A, D, E, and K. These are generally consumed along with fat-containing foods. The water-soluble vitamins include the B vitamins and vitamin C. These cannot be stored by the body and must be consumed frequently, usually every day. The only vitamin manufactured in our bodies is vitamin D. All others must be derived from the diet. Deficiencies in vitamin intake can cause different health problems.

BETA-CAROTENE

Introduction

Beta-carotene is one of several hundred carotenoids. Activity varies depending on the isomer. It is converted, in part, to vitamin A (retinol) at the GI tract and may contribute some antioxidant activity.

⦿ Beta-Carotene

Brand Names

Various

Generic Names

Beta-carotene, all-*trans*-beta-carotene, vitamin A

OTC

Dosage Forms

Tablet, capsule

Usage

Meet vitamin A intake requirement; reduce risk of cardiovascular disease, cancer, age-related macular degeneration, and cataracts

Pregnancy Category

Pregnancy category X (dose dependent). Excessive vitamin A during pregnancy may cause craniofacial malformations, as well as CNS, heart, and thymus abnormalities. Doses of > 6,000 units/day have not been established to be safe in pregnant women and should be avoided.

Dosing

- RAE = Retinol activity equivalent; 1 RAE = retinol 1 µg or dietary beta-carotene 12 µg; retinol 1 µg = 3.33 units of vitamin A
- Recommended dietary allowance (RDA):
  - Children 1 to 3 years: 300 µg/day (1000 units/day)
  - Children 4 to 8 years: 400 µg/day (1330 units/day)
  - Children 9 to 13 years: 600 µg/day (2000 units/day)
  - Males > 13 years: 900 µg/day (3000 units/day)
  - Females > 13 years: 700 µg/day (2330 units/day)
  - Pregnant females 14 to 18 years: 750 µg/day (2500 units/day)
  - Lactating females 14 to 18 years: 1200 µg/day (4000 units/day)
- Renal dosage adjustment: Not known

Adverse Reactions: Rare/Severe/Important

High doses may cause hepatotoxicity, carotenoderma (orange/yellow skin discoloration)

Major Drug Interactions

Drugs Affecting Beta-Carotene

Cholestyramine, mineral oil, orlistat, and proton pump inhibitors: Reduce absorption

Beta-Carotene's Effect on Other Drugs

- Carotenoids: Decreases bioavailability (e.g., lutein)
- Oral retinoids (e.g., isotretinoin): Increases risk of vitamin A toxicities

Counseling Point

Dietary content of beta-carotene is approximately 3 mg daily

Key Point

Doses of > 6,000 units/day have not been established to be safe in pregnant women and should be avoided

CALCIUM

Introduction

Calcium has a structural role in bone and teeth. It also has important roles in vascular, neuromuscular, and glandular function.

◉ Calcium

Brand Names

Calcium (Various), Cal-Lac, Caltrate, Calsorb, Citracal, Os-Cal, Tums

Generic Names

Calcium, calcium salts, calcium carbonate, citrate, etc.

OTC

Dosage Form

Tablet

Usage

Prevention or treatment of calcium deficits, management of osteoporosis, hypertension, premenstrual syndrome, reduction of risk of colon cancer

Pregnancy Category

Not assigned for most common oral forms of calcium, such as calcium carbonate; refer to dosing for pregnant women

Dosing

- 500 mg of elemental calcium 2 to 3 times daily
- Age 14 to 18 years:
  - 1300 mg daily
  - Pregnant or lactating: 1300 mg daily
- Age 19 to 50 years:
  - 1000 mg daily
  - Pregnant or lactating: 1,000 mg daily
- Age > 50 years: 1200 mg daily
- Tolerable upper intake level: 2500 mg daily from all sources
- Renal dosage adjustment: Not known

Adverse Reactions: Most Common

Nausea, constipation, flatulence

Adverse Reactions: Rare/Severe/Important

Renal insufficiency, nephrolithiasis, hypercalcemia

Major Drug Interactions

Drugs Affecting Calcium

- Corticosteroids: Decrease calcium status
- Loop diuretics: Increase urinary calcium loss
- Thiazide diuretics: Increase renal calcium reabsorption

Calcium's Effect on Other Drugs

- Etidronate, levothyroxine, oral fluoroquinolones, oral tetracyclines, iron, magnesium, levothyroxine, zinc: Decreases absorption; separate dosing by at least 2 hours to avoid this interaction
- Tamoxifen: Increases hypercalcemia risk

Counseling Points

- Avoid the following sources of calcium because of potential contaminants: Bone meal, dolomite, oyster shells (may be of risk in patients with severe shellfish allergy)
- Dose in terms of elemental calcium (see **Table 15.1**)
- Maximize calcium absorption by dividing doses (500 mg/dose maximum)
- Take with meals

TABLE 15.1 Dosing in Terms of Elemental Calcium

Calcium Salt	Elemental Calcium	Calcium (mg)/Salt (g)
Calcium carbonate	40%	400
Dibasic calcium phosphate	23%	230
Calcium citrate	21%	210
Calcium lactate	13%	130
Calcium gluconate	9%	90

CYANOCOBALAMIN

Introduction

Cyanocobalamin, or vitamin B_{12}, is essential in the maintenance of cellular integrity, particularly in disease states such as anemia, pregnancy, thyrotoxicosis, malignancy, liver, neurologic disorders, or kidney disease

⦿ Cyanocobalamin

Brand Names

CaloMist, Nascobal, Twelve-Resin

Generic Names

Cyanocobalamin, vitamin B_{12}

OTC

Dosage Forms

Tablet, injection, lozenge, intranasal solution

Usage

Prevention and treatment of vitamin B_{12} deficiency, treatment of pernicious anemia

Pregnancy Category

Pregnancy category A when using at the RDA or recommended dose for pregnant women; Category C at higher doses and intranasal dosage form

Dosing

- Recommended intake:
  - Adults: 2.4 µg/day
  - Pregnant women: 2.6 µg/day
  - Lactating women: 2.8 µg/day
- Vitamin B_{12} deficiency dosing:
  - Intranasal:
    - Nascobal: 500 µg in one nostril once weekly
    - CaloMist: Maintenance therapy (following correction of vitamin B_{12} deficiency) is 25 µg in each nostril daily; if suboptimal response, 25 µg in each nostril twice daily
  - Oral: 250 µg/day
  - IM, deep SUB-Q:
    - Initial dose: 30 µg/day for 5 to 10 days
    - Maintenance dose: 100–200 µg/month
- Pernicious anemia:
  - IM, deep SUB-Q:
    - Initial dose: 100 µg/day for 6 to 7 days; if improvement noted, administer the same dose on alternating days for seven doses, then every 3 to 4 days for 2 to 3 weeks
    - Maintenance dose: 100 µg/month
    - Alternative dosing: 1000 µg/day for 5 days followed by a maintenance dose of 500–1000 µg/month
  - Maintenance dose for a hematologic remission/correction of pernicious anemia:
    - Intranasal (Nascobal): 500 µg in one nostril once weekly
    - Oral: 1000–2000 µg/day
    - IM, deep SUB-Q: 100–1000 µg/month
  - Renal dosage adjustment: None

Adverse Reactions: Most Common

Injection-site reactions/redness with IM and deep SUB-Q injections

Adverse Reactions: Rare/Severe/Important

Congestive heart failure, polycythemia vera, paresthesias, pulmonary edema

Major Drug Interactions

Drugs Affecting Cyanocobalamin

Chloramphenicol: May diminish effect

Cyanocobalamin's Effects on Other Drugs

Alcohol: Heavy use/consumption > 2 weeks can impair absorption

Counseling Point

Use exactly as prescribed

ERGOCALCIFEROL

Introduction

Ergocalciferol, a vitamin D analog (Vitamin D2), is essential in the maintenance of vitamin D levels, particularly in women, to prevent osteoporosis and in patients with chronic kidney disease. (See also in this section, "Vitamin D" for information on Vitamin D3, also known as cholecalciferol).

Mechanism of Action for the Drug Class

Ergocalciferol stimulates calcium and phosphorous absorption from the small intestine and promotes secretion of calcium from bone to blood; it also promotes renal tubule resorption of phosphorous

◉ Ergocalciferol

Brand Name

Drisdol

Generic Name

Ergocalciferol

OTC

Dosage Forms

Capsule, liquid, tablet (Note: 1 µg = 40 international units [IU])

Usage

Prevention and treatment of vitamin D deficiency, treatment of refractory rickets, treatment of hypophosphatemia and hypoparathyroidism

Pregnancy Category

Category A when used at RDA; Category C at higher doses

Dosing

- Recommended intake:
  - Age 18 to 50 years: 5 µg/day
  - Age 51 to 70 years: 10 µg/day
- Osteoporosis prevention and treatment for adults age ≥ 50 years: 10 µg/day
- Vitamin D deficiency/insufficiency in patients with chronic kidney disease (CKD) [Kidney Disease Outcomes Quality Initiative guidelines for stage 3–4 CKD]:
  - Serum 25-hydroxyvitamin D level < 5 ng/ml: 50,000 IU/week for 12 weeks, then 50,000 IU/month
  - Serum 25-hydroxyvitamin D level 5–15 ng/ml: 50,000 IU/week for 4 weeks, then 50,000 IU/month
  - Serum 25-hydroxyvitamin D level 16–30 ng/ml: 50,000 IU/month
- Hypoparathyroidism: 625 µg to 5 mg/day orally
- Nutritional rickets and osteomalacia:
  - Adults with normal absorption: 25–125 µg/day
  - Adults with malabsorption: 250–7500 µg/day
- Renal dosage adjustment: None

Adverse Reactions: Most Common

Nausea, metallic taste in mouth, dry mouth

Adverse Reactions: Rare/Severe/Important

None

Major Drug Interactions

None

Counseling Point

Use exactly as prescribed

Key Point

For osteoporosis, adequate calcium supplementation is required with vitamin D analog supplementation

FERROUS SULFATE

Introduction

Ferrous sulfate is one of the most widely used iron supplements. It is widely used in the treatment of iron deficiency anemia.

Mechanism of Action for the Drug Class

These supplements replace the iron found in hemoglobin, myoglobin, and other enzymes

◉ Ferrous Sulfate

Brand Names

Feosol, Fer-Gen-Sol, Fer-In-Sol, Fer-Iron, Feratab, Slow-Fe

Generic Name

Ferrous sulfate

OTC

Dosage Forms

Elixir, liquid, tablet, extended-release tablet

Usage

Prevention and treatment of iron deficiency anemia

Pregnancy Category

Not assigned an FDA pregnancy risk category; assess risk vs benefit of therapy during pregnancy

Dosing

- Treatment of iron deficiency anemia:
  - Immediate-release formulations: 300 mg 2 to 4 times daily
  - Extended-release formulations: 250 mg 1 to 2 times daily
- Prophylaxis of iron deficiency: 300 mg daily
- Renal dosage adjustment: None

Adverse Reactions: Most Common

Constipation, dark stools, GI irritation, nausea, stomach cramping, vomiting, staining of teeth with liquid preparations

Adverse Reactions: Rare/Severe/Important

None

Major Drug Interactions

Drugs Affecting Iron

- Antacids: May decrease absorption of iron salts; consider therapy modification
- H_2-receptor antagonists: May decrease absorption of iron salts

Iron's Effect on Other Drugs

- Bisphosphonates: May decrease absorption
- Cefdinir: May decrease concentration, forming an insoluble cefdinir–iron complex. This may be objectively noted by a red-appearing, nonbloody stool. Avoid this combination if possible; if not possible, separate doses by several hours to minimize interaction.
- Dimercaprol: Contraindicated with iron salts because it may enhance nephrotoxicity
- Fluoroquinolone antibiotics (oral), tetracycline derivatives (oral): May decrease absorption of these antibiotics; separate doses by 2 to 4 hours to avoid this interaction
- Levodopa, methyldopa, levothyroxine, pancrelipase, phosphate supplements: May decrease absorption; separate doses by 2 to 4 hours to lessen this interaction

Counseling Points

- Take between meals for maximal absorption; try to take on empty stomach. Do not take with milk or antacids.
- Use exactly as prescribed
- Keep out of reach of children; iron toxicity is one of the leading accidental drug poisonings seen in young children
- Stool may turn black; this is important to recognize, particularly when you are on anticoagulants and/or antiplatelet agents. Be aware that black stool can also be an indication of blood in stool. Contact your healthcare provider if this occurs while taking anticoagulants or antiplatelet agents with iron supplements.
- If constipation occurs, try increasing fluids and foods with fruit and fiber. If constipation lasts > 3 to 4 days, contact your healthcare provider.

Key Points

- Foods, particularly grains, dietary fiber, tea, coffee, eggs, milk, and wines with tannins, may decrease oral iron salt absorption. Counsel patients to take on empty stomach if possible.
- The elemental iron content of ferrous sulfate is 20%; 324 mg of ferrous sulfate tablet contains 65 mg of elemental iron. Therefore, with special-formulated preparations (exsiccated), such as Feosol, a 200-mg tablet contains 65 mg of elemental iron. Slow-Fe, an oral exsiccated and time-released tablet, has 50 mg of elemental iron in a 160-mg tablet.
- Oral solution and elixir prescriptions should never be written in only volume (milliliters) because different concentrations of iron exist; use dosages in milligrams
- Use with caution in patients receiving multiple blood transfusions to prevent accidental iron overload/toxicity

FLUORIDES

Introduction

With more and more communities removing fluorides from drinking water, patients, particularly parents with young children, need to rely on oral fluoride supplementation to prevent dental caries.

Mechanism of Action for the Drug Class

Ionic forms of fluorine (fluorides) are cariostatic, inhibiting the bacteria implicated in causing dental cavities/caries. They also strengthen dental enamel.

Oral Fluorides

Brand Names

ACT, APF, CaviRinse, CavityShield, ControlRx, Duraphat Varnish, EtheDent, Fluor-A-Day, Fluorabon Drops, Fluorinse, Fluoritab, Fluorofoam, Flura-Drops, Gel-Kam, Gel-Kam DentinBloc, Just for Kids, Minute-Foam, Neutra-Foam, NeutraCare, OMNI, OrthoWash, PerioMed, Phos-Flur, PreviDent 5000 Plus, PreviDent, PreviDent Varnish, SF 5000 Plus, SF, Stop, Vanish Varnish

Generic Names

Sodium fluoride, tin fluoride, stannous fluoride

OTC

Dosage Forms

Lozenge, solution, chewable tablet, cream, foam, gel, oral rinse

Usage

Prevention of dental caries

Pregnancy Category B

Safe when taken per instructions of individual dental products. Tolerable upper daily limit is 10 mg; however, the American Dental Association (ADA) does not recommend supplemental fluoride during pregnancy.

Dosing

- Varies widely per product and dosage form; refer to label and instructions for individual products
- **Table 15.2** lists the oral dosage of supplemental fluoride (as a lozenge, chewable tablet, or solution) for children living in areas with drinking water that has insufficient quantities of fluoride (expressed in terms of fluoride ion)

Adverse Reactions: Most Common

Staining or pigmentation (e.g., yellow, brown, brown-black) of the teeth may result from topical application of concentrated solutions or gels of stannous fluoride, particularly in patients with poor oral hygiene

Adverse Reactions: Rare/Severe/Important

Consuming excessive amounts of fluorides can result in fluorosis (hypocalcification and hypoplasia) and osseous changes in children < 8 years of age, especially at levels of water fluoridation > 0.6 ppm. Dyspnea has occurred in asthmatic children using a 5% sodium fluoride solution. Hypersensitivity reactions.

Major Drug Interactions

Drugs Affecting Fluoride

Drugs/supplements that contain aluminum hydroxide, calcium salts, and magnesium hydroxide: May decrease bioavailability of oral fluorides. Do not take at the same time; separate by at least 2 hours.

Counseling Points

- Dairy products can reduce bioavailability of oral fluorides; do not ingest at the same time
- Follow instructions per product labeling
- Children in locations with adequate fluoride concentrations in the drinking water (> 0.6 ppm) do not need supplemental fluorides

Key Points

- Children in locations with adequate fluoride concentrations in the drinking water (> 0.6 ppm) do not need supplemental fluorides
- Although safe for pregnant women, the ADA does not recommend fluoride supplementation during pregnancy

TABLE 15.2 Fluoride Dosing for Children Based on Fluoride Concentration in Drinking Water

	Fluoride Ion Concentration in Drinking Water		
Age	**< 0.3 ppm**	**0.3–0.6 ppm**	**> 0.6 ppm**
0 to 6 months	None	None	None
6 months to 3 years	0.25 mg	None	None
3 to 6 years	0.5 mg	0.25 mg	None
6 to 16 years	1 mg	0.5 mg	None

FOLIC ACID

Introduction

Folic acid is a water-soluble B vitamin. Supplementation of folic acid in women who are pregnant or planning to become pregnant has significantly reduced the number of infants born with neural tube defects.

Mechanism of Action for the Drug Class

Folic acid is necessary for the formation of numerous enzymes and coenzymes in many metabolic systems, particularly in the formation of DNA and RNA bases (purines and pyrimidines). It is also required for the maintenance of red blood cell production.

◉ Folic Acid

Brand Names

Folvite, Folacin-800

Generic Name

Folic acid

OTC

Dosage Forms

Tablet, injectable

Usage

Treatment of megaloblastic (macrocytic) anemia due to folic acid deficiency, antenatal dietary supplement to prevent fetal neural tube defects

Pregnancy Category A

Dosing

- Treatment of folic acid deficiency: 0.4 mg daily
- Prevention of fetal neural tube defects in pregnant women: 0.4–0.8 mg daily. Women at high risk should receive 4 mg daily.

Adverse Reactions

Rare

Major Drug Interactions

Drugs Affecting Folic Acid

Methotrexate, trimethoprim, chloramphenicol, phenytoin, phenobarbital: Decrease effectiveness

Folic Acid's Effect on Other Drugs

Phenytoin, phenobarbital, primidone: Decreases effects

Contraindication

Treatment with folic acid in other megaloblastic anemias (pernicious anemia and vitamin B_{12} deficiency) without proper diagnosis can mask these anemias and lead to progression that can include irreversible nerve damage

Counseling Point

Take folic acid replacement only with the recommendation of a healthcare provider

Key Point

Decreases the incidence of fetal neural tube defects by > 50%; critical nutrient in prenatal care

RIBOFLAVIN

Introduction

Riboflavin, also known as Vitamin B_2, is a water soluble vitamin, and part of the flavins. Flavins have a critical role in numerous biochemical reactions. Riboflavin deficiency may be more common than appreciated and since symptoms of deficiencies can vary, it can go unrecognized. Symptoms of deficiency can include sore throat, mucositis, anemia, and seborrheic dermatitis.

Mechanism of Action for the Drug Class

Riboflavin is a key component of coenzymes involved in multiple metabolic pathways, including crucial energy-producing respiratory pathways. Riboflavin and flavins, in general, are also key cofactors in a number of mitochondrial redox reactions and function as electron transporters. Studies have also shown that a deficit in mitochondrial energy metabolism may also play a role in migraine pathogenesis, and clinical trials showed some benefit of using riboflavin at a high dose for migraine prophylaxis.

◉ Riboflavin

Brand Names

Generally incorporated in numerous multivitamin formulations, MiG relief (high-dose supplement for migraine prophylaxis)

Generic Name

Riboflavin, Vitamin B_2

OTC

Dosage Forms
Tablet, capsule

Usage
Migraine prophylaxis, general dietary supplement

Pregnancy Category A

Dosing
- RDA:
  - Male: 1.3 mg
  - Female: 1.1 mg
  - Pregnancy and Lactation: 1.4–1.6 mg daily
- Prophylaxis for migraine: 400 mg daily

Adverse Reactions
Rare

Major Drug Interactions
No significant interactions

Contraindication
No significant contraindications

Counseling Point
Take high dose riboflavin (for migraine prophylaxis) only with the recommendation of a healthcare provider

Key Point
Good dietary sources of riboflavin include milk, eggs, meats, fish, green vegetables, grains/breads, and yeast

THIAMINE

Introduction
Thiamine is a water-soluble B vitamin (B_1). Thiamine deficiency can cause two main types of syndromes: beriberi and Wernicke–Korsakoff syndrome. Beriberi manifestations can result in the development of peripheral neuropathies and motor impairments, as well as cardiac involvement, ranging from cardiomyopathy, to heart failure, to peripheral edema, to tachycardia. Wernicke–Korsakoff syndrome is the best known neurologic complication of thiamine deficiency with manifestations of encephalopathy (Wernicke's encephalopathy), and/or chronic neurologic deficit with impaired short-term memory loss and fabrication of imaginary experiences. Chronic alcoholics are more prone to Wernicke–Korsakoff syndrome, particularly Wernicke's encephalopathy due to marked thiamine deficiency.

Mechanism of Action for the Drug Class
Thiamine is an essential coenzyme in carbohydrate metabolism combining with ATP to form thiamine pyrophosphate. Numerous metabolic pathways require this cofactor, but thiamine also has a role in the initiation of nerve impulse propagation that is independent of its coenzyme functions.

◉ Thiamine

Brand Names
Contained is almost every multivitamin supplement

Generic Name
Thiamine, thiamin, Vitamin B1

OTC

Dosage Forms
Tablet, capsule, injectable (Rx only)

Usage
Part of a multivitamin supplement, prevention and treatment of thiamine deficiency, Wernicke's encephalopathy

Pregnancy Category A

Dosing
- RDA:
  - Adult females: 1.1 mg
  - Adult males: 1.2 mg
  - Pregnancy, lactation: 1.4 mg
- Treatment of thiamine deficiency (beriberi): 5–30 mg IM or IV 3 times daily, then 5–30 mg daily for 1 month
- Alcohol withdrawal syndrome: 100 mg/day IM or IV; if critically ill 100 mg daily IM or IV 3 times daily for several days, followed by 50–100 mg po daily
- Treatment for Wernicke's encephalopathy: Initial dosing of 500 mg IV 3 times daily for 3 days. If response is noted after 3 days, continue with 250 mg IM or IV daily for an additional 5 days or until clinical improvement.
- Prophylaxis dosing for Wernicke's encephalopathy: 250 mg IV once daily for 3 to 5 days

Adverse Reactions
Rare, hypersensitivity with parenteral product. Localized irritation with IM injection. No real syndrome of excessive thiamine exists since the kidney rapidly clears excessive thiamine.

Major Drug Interactions

Drugs Affecting Thiamine

Ethanol: Decrease effectiveness by decreasing absorption

Contraindications

Hypersensitivity to injectable thiamine

Counseling Point

Take thiamine replacement only with the recommendation of a healthcare provider

Key Point

Good dietary sources of thiamine include whole grains, legumes, corn flour, pecans, and spinach

VITAMIN C

Introduction

Vitamin C is an important vitamin. Many consumers take vitamin C supplements to reduce the severity and duration of the common cold.

Mechanism of Action for the Drug Class

Vitamin C is an essential cofactor in numerous biochemical reactions. It indirectly provides electrons to enzymes that require prosthetic metal ions in reduced form for their activity. It is an antioxidant in aqueous environments. It is a cofactor in the synthesis of carnitine, neurotransmitters, and collagen. Vitamin C exists in both reduced and oxidized forms.

◉ Vitamin C

Brand Names

Ascorbate-C, C Aspa Scorb, Ester-C, Vicks Vitamin C, and others

Generic Names

Vitamin C, L-ascorbic acid

OTC

Dosage Forms

Tablet, chewable tablet, capsule, powder

Usage

Improves wound healing, reduces symptoms of the common cold (unproven; anecdotal), prevents and treats scurvy, improves dietary iron absorption

Pregnancy Category A (at RDA levels) and C (at higher doses)

Dosing

- RDA:
  - Men: 90 mg daily
  - Women: 75 mg daily
  - Smokers: Increase RDA by 35 mg
- Renal dosage adjustment: Lower doses recommended in renal insufficiency

Adverse Reactions: Most Common

Nausea, abdominal cramps, flatulence, diarrhea

Adverse Reactions: Rare/Severe/Important

Renal consequences, including hyperoxaluria, risk of nephrolithiasis

Major Drug Interactions

Drugs Affecting Vitamin C

- Aspirin, ethanol: Reduce tissue saturation of vitamin C
- Oral contraceptives, tobacco smoke exposure: Increase clearance

Vitamin C's Effect on Other Drugs

- Cotrimoxazole: Increases bioavailability
- Estradiol/levonorgestrel: Increases clearance
- Warfarin: Decreases effect

Counseling Points

- Intestinal absorption and renal reabsorption are saturable processes, so doses > 200 mg should be divided to limit GI discomfort
- Tolerable upper intake level set at 2000 mg daily from all sources
- Chronic use of chewable vitamin C products may increase the risk of dental erosions and caries
- No difference in bioavailability or activity exists between natural and synthetic vitamin C

Key Points

- High daily doses may interfere with laboratory tests but may be assay-dependent:
  - Serum aspartate aminotransferase, bilirubin, creatinine, carbamazepine: False increase
  - Serum lactate dehydrogenase, uric acid, vitamin B_{12}, theophylline: False decrease
  - Guaiac test for occult blood: False negative
- Use with caution in patients with glucose-6-phosphate dehydrogenase deficiency
- For pregnant women, daily limits from all sources should be no greater than 2000 mg of vitamin C

VITAMIN D

Introduction

Vitamin D is essential for promoting calcium absorption in the gut and maintaining adequate serum calcium and phosphate concentrations. The most commonly used formulations for supplementation are vitamin D_3, also known as cholecalciferol; and vitamin D_2, also known as ergocalciferol (see monograph specifically for this product). Vitamin D_3 or cholecalciferol is a preferred method of supplementation by some clinicians and is discussed here in this monograph.

Brand Names

Vitamin D, D_3

Generic Name

Cholecalciferol

Rx and OTC

Dosage Forms

Capsule, tablet, liquid

Usage

Dietary supplement, treatment or prophylaxis of vitamin D deficiency, osteoporosis prevention and treatment

Pregnancy Category

When doses are consistent with the RDA, vitamin D analogs are pregnancy category A. Doses should not exceed the RDA in pregnant women. Doses greater than the RDA are considered to be pregnancy category C.

Dosing

- Age 18 to 50 years: 200 IU/day
- Age 51 to 70 years: 400 IU/day
- Age > 70 years: 600 IU/day

Contraindications

Hypercalcemia, hypersensitivity

Adverse Reactions: Most Common

None

Adverse Reactions: Rare/Severe/Important

Hypervitaminosis D is a severe adverse reaction. Signs and symptoms include hypercalcemia, resulting in headache, nausea, vomiting, lethargy, confusion, sluggishness, abdominal pain, bone pain, polyuria, polydipsia, weakness, cardiac arrhythmias (e.g., QT shortening, sinus tachycardia), soft tissue calcification, calciuria, and nephrocalcinosis.

Major Drug Interactions

Drugs Affecting Vitamin D

Mineral oil, orlistat, bile acid sequestrants: May decrease absorption of vitamin D analogs; separate dosing by 2 to 4 hours to lessen this interaction

Vitamin D's Effect on Other Drugs

Aluminum hydroxide and sucralfate: Increases serum concentrations; avoid concomitant use or separate by 2 to 4 hours to lessen this effect

Counseling Point

Take as directed

VITAMIN E

Introduction

Vitamin E is an important vitamin that protects cell membranes from oxidative damage, inhibits proliferation of smooth muscle, and decreases adhesion of platelets, leukocytes, and endothelial cells.

◉ Vitamin E

Brand Name

None

Generic Names

Vitamin E, tocopherols (alpha, beta, gamma, and delta), tocotrienols (alpha, beta, gamma, and delta)

OTC

Dosage Forms

Tablet, capsule

Usage

Vitamin E deficiency, prevention of cardiovascular disease morbidity and mortality (not labeled/approved), slowing progression of neurologic disorders (e.g., dementia, Parkinson's disease [not labeled/approved])

Pregnancy Category A (at RDA levels) and C (at higher doses)

Vitamin E crosses the placenta. Maternal serum concentrations of alpha-tocopherol increase with lipid

concentrations as pregnancy progresses; however, placental transfer remains constant. Additional supplementation is not needed in pregnant women without deficiency.

Dosing

- RDA: 15 mg daily of alpha-tocopherol
- Tolerable upper intake: 1000 mg daily from all alpha-tocopherol sources
- Renal dosage adjustment: None

Adverse Reactions: Most Common

GI upset

Adverse Reactions: Rare/Severe/Important

Increased risk of bleeding and hemorrhagic stroke, thrombocytopenia

Major Drug Interactions

Drugs Affecting Vitamin E

- Cholestyramine, orlistat, mineral oil: Decrease absorption
- Fish oil: Increases vitamin E requirements

Vitamin E's Effect on Other Drugs

Warfarin, antiplatelet agents, insulin, digoxin: Increases effects

Counseling Point

Take as prescribed

Key Points

- The predominant form of vitamin E in the diet is gamma-tocopherol. In the body, it is alpha-tocopherol. Select a product containing both forms.
- Bioavailability is enhanced in the presence of food containing some dietary fat
- Use a water-miscible formulation in patients with malabsorptive disorders
- Although IUs are no longer recognized as a dosing unit for vitamin E, it is still found in product labeling; this requires conversion to milligram alpha-tocopherol for comparison to dosing recommendations:
  - mg = IU all-*rac*-alpha-tocopherol as acetate/succinate/2.2
  - mg = IU RRR-alpha-tocopherol as acetate/succinate/1.5

VITAMIN K

Introduction

Vitamin K, also known as phytonadione, is a fat-soluble vitamin and is essential in the formation of key coagulation factions (namely Factors II, VII, IX, and X). Rather than be used primarily as a dietary supplement per se, it is used therapeutically for correction of coagulopathies due to vitamin K deficiencies, as seen in liver disease and even malnutrition; but most often, it is used for correction of hypoprothrombinemia and coagulopathies from drugs that are vitamin K antagonists (VKA). Warfarin is the main VKA used in the United States.

◉ Vitamin K

Brand Name

Mephyton

Generic Names

Vitamin K, phytonadione

Rx (generally not used/available as sole OTC agent)

Dosage Forms

Tablet, parenteral (as a parenteral, it does not meet the criteria as a dietary supplement and is classified as a drug). According to the manufacturer, SUB-Q is the preferred route of administration; however, a less-predictable absorption occurs via this route. IM route is to be avoided due the risk of hematomas. The IV route (diluted and infused over 15 to 30 minutes; never undiluted or rapid IV push) is preferred according to the American College of Chest Physicians (ACCP) for reversal of major bleeding due to coagulopathy from VKAs. (See notes on IV administration in Key Points and Black Box Warning).

Usage

Vitamin K nutritional deficiency, Hypoprothrombinemia and coagulopathy reversal secondary to warfarin and other VKAs, hemorrhagic disease of the newborn

Pregnancy Category C

Vitamin K crosses the placenta. The dietary requirements of vitamin K are the same in both pregnant and nonpregnant women. In instances in which mothers are concomitantly using certain anticonvulsants known to have strong liver enzyme induction (i.e., phenytoin, carbamazepine) during the third trimester of pregnancy, supplemental vitamin K may be recommended because liver enzyme induction caused by these agents may lead to maternal/fetal vitamin K deficiencies and hemorrhagic disease of the newborn due to this deficiency.

Dosing

- RDA: 120 µg daily for males, 90 µg/day females
- Hemorrhage disease of the newborn: 0.5–1 mg within 1 hour of birth for prophylaxis, and 1 mg per dose per day for treatment
- Use of vitamin K for the management of supratherapeutic INR
- Renal dosage adjustment: None

Adverse Reactions: Most Common

GI upset

Adverse Reactions: Rare/Severe/Important

Thrombosis (overcorrection of hypoprothrombinemia), hypersensitivity/anaphylactoid reactions (injection)
Black Box Warning: Severe reactions, including fatalities, have occurred during and immediately after intravenous injection of phytonadione, even when precautions have been taken to dilute the phytonadione and to avoid rapid infusion. Severe reactions, including fatalities, have also been reported following intramuscular administration. Typically, these severe reactions have resembled hypersensitivity or anaphylaxis, including shock and cardiac or respiratory arrest. Some patients have exhibited these severe reactions on receiving phytonadione for the first. Therefore, restrict IV and IM routes to those situations where the subcutaneous route is not feasible and the serious risk involved is considered justified.

Major Drug Interactions

Drugs Affecting Vitamin K

Cholestyramine, orlistat, mineral oil: Decrease absorption

Vitamin K's Effect on Other Drugs

Warfarin: Vitamin K can diminish the anticoagulant of warfarin

Counseling Point

Take as prescribed

Key Points

- **Black Box Warning:**
  - Severe reactions, including fatalities, have occurred during and immediately after intravenous injection of phytonadione, even when precautions have been taken to dilute the phytonadione and to avoid rapid infusion. Severe reactions, including fatalities, have also been reported following intramuscular administration. Typically, these severe reactions have resembled hypersensitivity or anaphylaxis, including shock and cardiac or respiratory arrest. Some patients have exhibited these severe reactions on receiving phytonadione for the first. Therefore, restrict IV and IM routes to those situations where the subcutaneous route is not feasible and the serious risk involved is considered justified.
- When given parenterally by the IV route, do not administer an undiluted product rapidly "push." Recommend to dilute vitamin K in 50 ml of dextrose 5% or normal saline and administer IV over 15 to 30 minutes.

INR	Bleeding Present	Recommendation
> Therapeutic to 5.0	No	Lower warfarin dose or omit a dose and resume warfarin at a lower dose when INR is in therapeutic range. No dose reduction if INR is mildly supratherapeutic.
> 5.0 to 9.0	No	Omit the next one to two doses of warfarin, monitor INR more frequently, and resume treatment at a lower dose when INR is in therapeutic range, or omit a dose and administer 1 to 2.5 mg of oral vitamin K.
> 9.0	No	Hold warfarin and administer 2.5 to 5 mg of oral vitamin K. Monitor INR more frequently and administer more vitamin K, as clinically warranted. Resume warfarin at a lower dose when INR is in therapeutic range.
Any	Serious or life-threatening bleeding	Hold warfarin. Administer 10 mg vitamin K diluted and by slow IV infusion. Supplement with four-factor prothrombin complex concentrate (4-factor-PCC) or fresh frozen plasma.

REVIEW QUESTIONS

1. Which of the following herbal supplements is touted for its cholesterol-lowering capabilities, mainly because it possesses pharmacologic properties similar to HMG co-reductase inhibitors?
   a. St. John's wort
   b. Chondroitin
   c. Valerian
   d. Red yeast rice

2. Excessive consumption of this product/supplement can easily lead to dyslipidemia?
   a. Coenzyme-Q
   b. Coconut oil
   c. The fat soluble vitamins, particularly vitamin D
   d. Chondroitin, when it's derived from cattle trachea vs shark cartilage

3. Which of the following herbal supplements is used as a calmative or sleep aid?
   a. Valerian
   b. Feverfew
   c. Echinacea
   d. Black cohosh

4. Remifemin and EstroSoy products contain which of the following natural supplements?
   a. Black cohosh
   b. Tocopherol
   c. Asian ginseng
   d. Siberian ginseng

5. Which route of administration of vitamin K is MOST likely to be associated with the Black Box Warning regarding an anaphylaxis-like reaction?
   a. Rapid IV push
   b. IM
   c. SUB-Q
   d. Oral

6. Which of the following dietary supplements would be expected to be found as a main ingredient in a branded product called Hydroxycut?
   a. Riboflavin
   b. Chondroitin
   c. Green coffee bean phenols
   d. Garcinia cambogia

7. Kava should be avoided due to its risk of:
   a. Liver toxicity.
   b. CYP450 Drug interactions.
   c. Memory loss.
   d. Allergic interstitial nephritis

8. Which of the following dietary supplements is used to support joint health?
   a. Melatonin
   b. Valerian
   c. Chamomile
   d. Glucosamine

9. Iron salts in dietary supplements may decrease the absorption of which of the following, if taken concomitantly?
   a. Levothyroxine
   b. Oral ciprofloxacin
   c. Oral levofloxacin
   d. All of the above

10. Coagulopathy and hypoprothrombinemia can result from a deficiency of which of the following in patients with liver disease?
    a. Vitamin A
    b. Vitamin B_{12}
    c. Vitamin C
    d. Vitamin K

11. Interactions with which of the following may increase therapeutic failure with drugs such as cyclosporine and protease inhibitors?
    a. Gingko biloba
    b. Glucosamine
    c. Valerian
    d. St. John's wort

12. A patient with HIV is on a protease inhibitor-containing regimen. Which of the following dietary supplements should this patient avoid or use only after consultation with the appropriate healthcare provider, due to a significant drug interaction from enzyme induction leading to decreased concentration of the protease inhibitor?
    a. St. John's wort
    b. Echinacea
    c. Probiotics that contain *Lactobacillus acidophilus*
    d. All of the above

13. Which of the following should be taken in a higher amount than the RDA to lessen the chance of fetal neural tube malformations in pregnant women?
    a. Vitamin C
    b. Thiamine
    c. Folic acid
    d. Vitamin B_{12}

14. If a patient who is on theophylline significantly increases his or her daily intake of caffeine, all the following side effects can be expected *except*:

- **a.** Tremors/"jitteriness"
- **b.** Palpitations
- **c.** Sinus tachycardia
- **d.** Urinary retention from excess anticholinergic effects

15. Wernicke's encephalopathy is generally seen in alcoholics who have a deficiency with which vitamin?

- **a.** Vitamin D
- **b.** Thiamine
- **c.** Vitamin K
- **d.** Vitamin A

16. Patients with liver disease sometimes use this supplement to promote a healthier liver. What is this supplement?

- **a.** Milk thistle
- **b.** Nutmeg
- **c.** Valerian
- **d.** Kava kava

17. Which of the following dietary supplements is given primarily to people with migraines because of its anti-inflammatory properties?

- **a.** Horse chestnut
- **b.** Ma huang
- **c.** Feverfew
- **d.** Milk thistle

18. A very over-hyped interaction with warfarin is associated with this dietary supplement; however, actual pharmacokinetic studies do not demonstrate such an interaction. What is this supplement?

- **a.** Vitamin K
- **b.** Cranberry
- **c.** St. John's wort
- **d.** Riboflavin

19. For which of the following indications do most consumers use ginger supplements?

- **a.** Flatulence
- **b.** Heartburn
- **c.** Constipation
- **d.** Urinary retention

20. Although touted as the "fountain of youth" hormone, which of the following may cause some serious side effects, such as gynecomastia in males and hepatotoxicity?

- **a.** DHEA
- **b.** Melatonin
- **c.** Bitter orange
- **d.** Milk thistle

21. Which of the following dietary supplements is formed from a pineal gland hormone and is touted to help regulate sleep cycles?

- **a.** Melatonin
- **b.** DHEA
- **c.** Chondroitin
- **d.** Glucosamine

22. Synephrine is the active chemical ingredient in which of the following dietary supplement?

- **a.** Bitter orange
- **b.** Kava
- **c.** Garcinia cambogia
- **d.** Milk thistle

23. Ingesting large quantities of grapefruit juice may increase toxicities with which of the following dietary supplements?

- **a.** Red yeast rice
- **b.** Horse chestnut
- **c.** Iron salts
- **d.** St. John's wort

24. Which of the following dietary supplements was thought to help prevent statin-induced myopathies until clinical studies showed no real benefit for this indication?

- **a.** Creatine
- **b.** Saw palmetto
- **c.** Co-enzyme Q
- **d.** Flaxseed oil

25. Which vitamin has been used in migraine prophylaxis?

- **a.** Riboflavin
- **b.** Vitamin E
- **c.** Vitamin C
- **d.** Thiamine

26. What is the maximum suggested daily intake of caffeine recommended from all sources for women who are pregnant?

- **a.** ≤ 65 mg daily
- **b.** ~ 100 mg daily
- **c.** ≤ 200 mg daily
- **d.** No more than 1000 μg daily

27. No Doz Maximum Strength and Vivarin contain primarily which dietary supplement?

- **a.** Iron
- **b.** DHEA
- **c.** Caffeine
- **d.** Melatonin

28. What is the primary reason that consumers use cranberry supplements?

- **a.** Prevention of urinary tract infections
- **b.** Prevention of gout attacks
- **c.** Hot flashes associated with menopause
- **d.** To thicken hair growth

29. Cholecalciferol is an analog of which of the following vitamins?

- **a.** Vitamin A
- **b.** Vitamin B_6
- **c.** Vitamin C
- **d.** Vitamin D

30. Which of the following dietary supplements or ingredients would be *least* likely to be found in a product that is used for weight loss and/or exercise endurance/"body-building"

- **a.** Garcinia cambogia
- **b.** Bitter orange
- **c.** Caffeine
- **d.** Flaxseed oil

CHAPTER 16

Biologic and Immunologic Agents

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VACCINES

Introduction

Vaccines are one of the most effective methods of disease prevention available. Vaccines contain the antigens or parts of antigens from pathogens that cause diseases but are either killed or greatly weakened. They are produced and used for diseases that tend to cause premature deaths or have a costly impact, such as increased physician visits or hospitalizations. Vaccines are available for a variety of infections, including polio, measles, diphtheria, pertussis (whooping cough), rubella (German measles), mumps, tetanus, and *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae*, varicella zoster, and influenza. The main adverse effect of vaccines is a local injection-site reaction (erythema, tenderness, pain, swelling, hematoma, and pruritus). Allegations of vaccine-related autism have been shown to be false, but the fear has led many people to avoid vaccines that would otherwise benefit them. As a result, some vaccine-preventable illnesses have begun to reemerge in developed countries.

Mechanism of Action for the Drug Class

Vaccines induce active immunity by introducing antigens into a host, which stimulates a primary immune response. Vaccines can be live-attenuated or inactivated and can include whole or part of a bacteria or virus. If the patient is subsequently exposed to the pathogen, a secondary immune response is mounted, leading to the production of antibodies. This results in immunity to the disease over the lifetime for live attenuated vaccines. Multiple "booster" doses of inactivated vaccines are needed to confer lifelong immunity.

Adverse Reactions for the Drug Class: Most Common

- Injectable vaccines: Injection-site reactions (pain, redness, and swelling)
- Most vaccines: Drowsiness, irritability, fever, crying

Adverse Reactions for the Drug Class: Rare/Severe/Important

- Allergic hypersensitivity reactions, ranging from rashes to anaphylaxis, are possible. Syncope can occur after vaccination.

Major Drug Interactions for the Drug Class

Drugs Affecting Vaccines

Immunosuppressants may diminish the therapeutic effect of vaccines

Members of the Drug Class

In this section: Diphtheria, tetanus toxoids, and acellular pertussis vaccine (DTaP); *H. influenzae* (Hib) vaccine; hepatitis B vaccine; influenza virus vaccine; human papillomavirus (HPV) vaccine; inactivated poliovirus (IPV) vaccine; measles, mumps and rubella virus vaccine (MMR); meningococcal vaccine; rotavirus vaccine; pneumococcal conjugate vaccine (13-valent); pneumococcal polysaccharide vaccine (23-valent); tetanus toxoid; reduced diphtheria toxoid and acellular pertussis vaccine (Tdap); varicella vaccine; zoster vaccine
Others: Numerous others

◉ Diphtheria, Tetanus Toxoids, and Acellular Pertussis Vaccine (DTaP)

Brand Name

Daptacel, Infanrix

Generic Name

Diphtheria, tetanus toxoids, and acellular pertussis vaccine

Rx Only

Dosage Form

Injection

Usage

Provision of active immunity for the prevention of disease from diphtheria, tetanus, and pertussis for infants and children 6 weeks to < 7 years

Pregnancy Category B/C (Manufacturer Specific)

Dosing

0.5 ml IM per dose, total of 5 doses administered as follows:

- First 3 doses, usually administered at 2, 4, and 6 months of age
- Fourth dose: Given at 15 to 20 months of age, at least 6 months after the third dose
- Fifth dose: Given at 4 to 6 years of age, prior to starting school or kindergarten

Contraindications

The vaccine is contraindicated in individuals with a progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or encephalopathy without known cause within 7 days of a pertussis vaccine

Essential Monitoring Parameters

- In children, monitor for fever, irritability and drowsiness following the administration of the vaccine. Very rarely, high fever, febrile seizures, and persistent crying occur following vaccination.
- Monitor for shortness of breath, lip swelling, and rash or hives, which may occur rarely after administration of the vaccine

Counseling Point

Injection-site reactions and fever are the most common adverse effects from the vaccine

Key Points

- The diphtheria, tetanus toxoids, and acellular pertussis vaccine is administered as a series to all infants at age 2, 4, 6 and 15 to 18 months. Booster vaccinations are recommended every 10 years.
- Adacel is formulated with the same antigens found in Daptacel but with reduced quantities of pertussis and tetanus. It is intended as a booster in children and adults and not for primary immunization.
- Boostrix is formulated with the same antigens found in Infanrix but in reduced quantities. It is intended as a booster for children and adults and not for primary immunization.
- Administer IM in the anterolateral aspect of the thigh or deltoid muscle of the upper arm

◉ *H. influenzae* Type B Vaccine (Hib)

Brand Names

ActHIB; Hiberix; PedvaxHIB

Generic Name

Haemophilus b conjugate vaccine

Rx Only

Dosage Form

Injection

Usage

Active immunization for the prevention of invasive disease caused by *H. influenzae* type b

Pregnancy Category C

Dosing

- Infants 6 weeks to 6 months:
  - ActHIB, Hiberix: 0.5 ml IM for 3 doses at 2, 4, and 6 months old
  - PedvaxHIB: 0.5 ml IM for 2 doses at 2 and 4 months of age
- Booster dose at age 12 to 15 months (at least 8 weeks after most recent Hib vaccine) or high-risk patients: 0.5 ml IM

Contraindications

Hypersensitivity to *Haemophilus* b polysaccharide, tetanus toxoid-containing vaccine (Hiberix and ActHIB only)

Essential Monitoring Parameters

- Syncope for 15 minutes following administration; in children, also monitor for fever, irritability, and drowsiness. Very rarely, high fever, febrile seizures, and persistent crying occur following vaccination.
- Monitor for shortness of breath, lip swelling, and rash or hives, which may occur rarely after administration of the vaccine

Counseling Points

- Injection-site reactions and fever are the most common adverse effects from the vaccine
- Report any chest tightness;wheezing; swelling of the lips, face, tongue, or throat; or seizures to the healthcare provider immediately
- Administered intramuscularly into the anterolateral thigh or deltoid

Key Points

- Hib vaccine is also available in combination with DTaP /IPV as Pentacel and with Neisseria meningitides serogroups C and Y as MenHibrix
- Administer a 2- or 3-dose primary series, depending on product used, starting at 2 months of age with a booster dose at 12 to 15 months of age
- Patients with the following high-risk conditions may require additional doses:
  - Chemotherapy recipients and with anatomic or functional asplenia (including sickle cell disease), HIV, immunoglobulin deficiency, early component complement deficiency, recipients of hematopoietic stem cell transplant
- Do not administer to anyone younger than 6 weeks of age.

Hepatitis B Vaccine

Brand Names
Engerix-B, Recombivax HB

Generic Name
Hepatitis B vaccine

Rx Only

Dosage Form
Injection

Usage
Provision of active immunity for the prevention of infections caused by the hepatitis B vaccine

Pregnancy Category C

Dosing
- Pediatrics/adolescents: 0.5 ml IM for 3 doses administered at 0, 1, and 6 months
- Adults: 1 ml IM for 3 doses administered at 0, 1, and 6 months

Contraindications
Consider deferring the hepatitis B vaccine in patients with moderate to severe acute febrile illness.

Essential Monitoring Parameters
Monitor for syncope for 15 minutes following administration. In preterm infants, consider respiratory monitoring for 48 to 72 hours after administration.

Counseling Points
- Tell your doctor if you have an infection or an illness with a fever
- Report any signs and symptoms of wheezing, rash or hives, or swelling of the mouth as soon as possible

Key Points
- The following populations should receive the hepatitis B vaccine:
  - All neonates before hospital discharge
  - All unvaccinated infants and children
  - Unvaccinated adults who are sexually active with > 1 sexual partner in a 6-month period, men who have sex with men, injection drug users
  - Healthcare personnel and public safety workers with exposure to blood or body fluids
  - Patients with end-stage renal disease, HIV, chronic liver disease, and adults with type 1 or type 2 diabetes mellitus
- The hepatitis B vaccine is administered in a series of 3 injections, intramuscularly. The formulations of the hepatitis B vaccine differ in terms of concentration (µg/ml). However, when dosed in terms of volume (ml), the dose of Engerix-B and Recombivax HB are the same.

Human Papillomavirus (HPV) Vaccine

Brand Name
Cervarix, Gardasil, Gardasil 9

Generic Name
Human Papillomavirus, bivalent, human papillomavirus quadrivalent, human papillomavirus 9-valent

Rx Only

Dosage Form
Injection

Usage
- Cervarix: Provision of active immunity for the prevention of HPV types 16 and 18: Cervical cancer and cervical intraepithelial neoplasia (CIN) in females 9 to 25 years of age
- Gardasil: Provision of active immunity for the prevention of cervical, vulvar, vaginal, and anal cancer caused by HPV types 16 and 18; genital warts caused by HPV types 6 and 11 in females 9 to 16 years of age. In males ages 9 to 26 years of age, provision of active immunity for anal cancer caused by HPV types 16 and 18; genital warts caused by HPV types 6 and 11.
- Gardasil 9: Provision of active immunity for the prevention of cervical, vulvar, vaginal, and anal cancer, caused by HPV types 16, 18, 31, 33, 45, 52, and 58 and genital warts caused by HPV types 6 and 11 in females 9 to 26 years of age. In males 9 to 26 years of age, provision of active immunity for anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58 and genital warts caused by HPV types 6 and 11.

Pregnancy
Animal reproduction studies did not reveal any adverse events. In pregnancies detected within 30 days of vaccination, no congenital abnormalities were noted. It is recommended to delay the vaccination series until pregnancy is completed.

Dosing
- Cervarix: 0.5 ml IM per dose for a total of 3 doses; administer second and third doses 1 and 6 months after initial dose
- Gardasil: 0.5 ml IM per dose for a total of 3 doses; administer second and third doses 2 and 6 months after the first dose
- Gardasil 9: 0.5 ml IM at 0, 2, and 6 months

Major Drug Interactions
Drugs Affecting Human Papillomavirus Vaccine

Immunosuppressants: May diminish the effect of the vaccine

Contraindications
Severe allergic reactions to yeast, which is a component of the vaccine (Gardasil, Gardasil-9)

Essential Monitoring Parameters

Gynecologic screening exam, papillomavirus test per guidelines; screening for cervical cancer should continue as recommended following vaccination (females). Screening for HPV is not required prior to vaccination. Observe for syncope for 15 minutes following administration.

Counseling Point

The most common adverse events associated with the vaccine are injection-site reactions (pain, redness, swelling) and fatigue, myalgias and arthralgias

Key Points

- Ideally, administration of the vaccine should occur prior to potential HPV exposure, which is why the vaccines are recommended before most people become sexually active. This counseling point may help to explain to reluctant parents why a vaccine for a sexually transmitted illness is given to preteenage children.
- Typically, the first dose is administered at age 11 to 12 years; for patients with any history of sexual abuse or assault, vaccination should be started at 9 years
- Cervarix, Gardasil, and Gardasil 9 contain the proteins HPV16L1 and HPV18L1, which cause > 70% of invasive cervical cancer. The vaccines differ in that Gardasil also contains HPV6L1 and HPV11L1 proteins, which protect against 75% to 90% of genital warts. Gardasil 9 adds HPV31L1, HPV33L1, HPV45L1, HPV52L1, and HPV58L1. The vaccines also differ in their preparation and the adjuvants used.
- The vaccine does not provide protection against HPV types to which a person has been previously exposed or HPV types not contained in the vaccine

◉ Inactivated Poliovirus Vaccine (IPV)

Brand Names

IPOL

Generic Name

Poliovirus vaccine (inactivated)

Rx Only

Dosage Form

Injection

Usage

Active immunization for the prevention of poliomyelitis caused by poliovirus types 1, 2, and 3

Pregnancy

Animal reproduction studies have not been conducted. It is not known whether the vaccine can cause fetal harm or affect reproduction capacity

Dosing

- Primary series: 0.5 ml SUB-Q or IM 8 or more weeks apart usually at ages 2, 4, and 6 to 18 months
- Booster dose at 4 to 6 years of age: 0.5 ml SUB-Q or IM

Contraindications

Hypersensitivity to 2-phenoxyethanol, formaldehyde, neomycin, streptomycin, and polymyxin B

Essential Monitoring Parameters

- Syncope for 15 minutes following administration; in children, also monitor for fever, irritability, and drowsiness. Very rarely: High fever, febrile seizures, and persistent crying occur following vaccination.
- Monitor for shortness of breath, lip swelling, and rash or hives, which may occur rarely after administration of the vaccine

Counseling Points

- Injection-site reactions and fever are the most common adverse effects from the vaccine.
- Report any chest tightness, wheezing, swelling of the lips, face, tongue or throat, or seizures to the healthcare provider immediately
- IM and SUB-Q administered to mid-lateral aspect of the thigh in infants and small children, deltoid to older children and adults

Key Points

- Administer a 4–dose series of IPV at ages 2, 4, 6, through 18 months, and 4 through 6 years of age. The final dose in the series should be administered on or after the fourth birthday and at least 6 months after the previous dose.
- IPV is available in combination with DTaP/Hep B (Pediarix), DTaP/Hib (Pentacel), and DTaP (Kinrix)
- Use of minimum age (6 weeks) and minimum intervals (4 weeks) during the first 6 months of life should only be done in patients with imminent exposure to circulating poliovirus

◉ Influenza Virus Vaccine

Brand Names

Inactivated: Fluarix, Fluzone, Afluria, FluLaval, Fluvirin, Flucelvax, Fluad, FluLaval
Live attenuated: FluMist

Generic Name

Influenza virus vaccine

Rx Only

Dosage Forms

Injection (inactivated), intranasal solution (live attenuated)

Usage

Provision of active immunity for the prevention of infections caused by influenza virus subtype A and B strains for people 6 months of age and older

Pregnancy Category B/C (Inactivated—Manufacturer Specific) and B (Live Attenuated)

Dosing

- Inactivated: 45 µg/0.5 ml IM (one dose per season)
- Live attenuated: 0.1 ml intranasal in each nostril (one dose per season)

Adverse Reactions: Most Common

- Inactivated: Pain and redness at the injection site, muscle aches, fatigue, headache
- Live attenuated: Runny nose or nasal congestion in all ages; fever in children 2 to 6 years of age; sore throat in adults; headache; fatigue

Adverse Reactions: Rare/Severe/Important

Life-threatening allergic reactions (very rare)

Major Drug Interactions

Drugs Affecting Influenza Virus Vaccine

Pneumococcal Conjugate Vaccine (13-Valent): May diminish the therapeutic effect of the inactivated vaccine

Influenza Virus Vaccine's Effect on Other Drugs

Aspirin-containing products: Avoid aspirin-containing therapy in children and adolescents during the first 4 weeks after vaccination with the live attenuated vaccine due to risk of Reye's syndrome

Contraindications

With live attenuated vaccine, avoid concomitant use of antiviral agents active against influenza A or B viruses. All formulations except Flucelvax cannot be used in patients with severe allergic reactions to egg proteins (worse than hives). Do not use the live attenuated vaccine in children 2 to 17 years of age receiving aspirin therapy.

Essential Monitoring Parameter

For individuals who report a history of egg allergy but for whom it was determined that the inactivated vaccine can be used, observe for at least 30 minutes after administration of vaccine. This is not an issue with Flucelvax, which is not cultured from eggs.

Counseling Points

- Get vaccinated every year as soon as the flu season vaccine becomes available in your community
- Consult your healthcare provider before receiving the flu vaccine if you have an egg allergy, a history of Guillain–Barré syndrome, or are pregnant. If you have egg allergies worse than hives, you should not receive the influenza vaccination with most available formulations.

Key Points

- Because the dominant influenza strains change each year, annual vaccination is required. Vaccine efficacy is dependent on the degree of a match between the strains in the vaccine and those that circulate in the community. Unfortunately, the vaccine strains are chosen well before influenza season and are based on the predominant strains from the season before.
- Everyone who is at least 6 months of age should get a flu vaccine in the absence of a contraindication
- Avoid use of intranasal flu vaccine (live attenuated) in pregnant or immunosuppressed patients
- An injectable flu vaccine and a nasal spray flu vaccine are available and are approved for different ages:
  - Regular flu shot: Approved for use in people ≥ 6 months of age
  - Flucelvax: Approved for use in people ≥ 18 years of age
  - High-dose flu shot (Fluzone High-Dose): Approved for use in people ≥ 65 years of age
  - Intradermal flu (Fluzone Intradermal) shot: Approved for use in people 18 to 64 years of age
  - Intranasal flu vaccine (FluMist): Approved for people 2 to 49 years of age

Measles, Mumps, and Rubella (MMR) Virus Vaccine

Brand Name

M-M-R II

Generic Name

Measles, mumps, and rubella virus vaccine

Rx Only

Dosage Form

Injection

Usage

Provision of active immunity for the prevention of measles, mumps, and rubella in patients ≥ 12 months of age

Pregnancy Category C

Dosing

0.5 ml SUB-Q per dose, 1 or 2 doses administered at least 28 days apart

Adverse Reactions: Rare/Severe/Important

Febrile seizures have occurred rarely in children following administration of the vaccine. Hypersensitivity reactions, including anaphylaxis and anaphylactoid reactions have been reported rarely in individuals receiving the vaccine with an allergic history.

Major Drug Interactions

Measles Mumps Rubella Virus Vaccine's Effect on Other Drugs

Tuberculin Tests: If the measles, mumps, and rubella vaccine has been recently administered, a PPD test should not be scheduled for at least 4 to 6 weeks following the administration of the vaccine

Contraindications

The vaccine is contraindicated in patients with a gelatin or neomycin allergy, which are both components of the vaccine. Individuals with a history of anaphylactoid or anaphylactic reactions to egg ingestion may be at increased risk of hypersensitivity reactions to this vaccine. Measles mumps rubella vaccine is contraindicated in patients with suppressed immune systems (i.e., HIV, malignancies), as well as pregnancy.

Essential Monitoring Parameters

- Monitor for fever and rash in the month following measles mumps rubella vaccine
- Monitor for shortness of breath, syncope, and hives immediately following administration of the vaccine, particularly in patients with history of hypersensitivity to eggs

Counseling Points

- Tell your doctor if you have a history of allergic reactions to eggs
- You may experience burning or stinging at the injection site
- Tell your doctor if you experience any rash, hives, shortness of breath, or dizziness following administration of the vaccine

Key Points

- The measles mumps and rubella virus vaccine is a live attenuated vaccine administered in most cases in two doses, 28 days apart
- Adults born prior to 1957 are considered to be immune to measles mumps rubella except women of childbearing potential. All women of childbearing potential should receive at least one dose of the measles mumps rubella vaccine.
- The measles mumps rubella vaccine is indicated for all people born in 1957 or later or in those who lack documentation of the infection by history or antibody titers. High-risk groups include children, college students, international travelers, and healthcare workers who were born in 1957 or later.
- The measles mumps rubella vaccine is contraindicated in pregnant and immunocompromised patients
- Caution is recommended in patients with a history of immediate hypersensitivity/anaphylactic reactions following egg ingestion, as the vaccine may contain trace amounts of chick embryo antigen
- The measles mumps rubella vaccine is well tolerated, and the most common adverse reactions include fever (5% to 15%) and rash (5%). These can occur 5 to 12 days postvaccination and can last from 2 to 5 days.

◉ Meningococcal ACWY Conjugate Vaccine

Brand Names

Menactra, Menveo

Generic Name

Meningococcal groups A, C, Y, and W-135 conjugate vaccine

Rx Only

Dosage Form

Injection

Usage

Active immunization for the prevention of invasive disease caused by *Neisseria meningitidis* serogroups A, C, Y, and W-135

Pregnancy Category B

Dosing

- Menactra
  - Primary vaccination for patients at increased risk of meningococcal disease:
    - Age 9 to 23 months: 2 doses of 0.5 ml IM 3 months apart
    - Age 2 to 55 years: 0.5 ml IM single dose
  - Booster vaccination
    - Age 15 to 55 years at increased risk for meningococcal disease: 0.5 ml IM single dose if at least 4 years have elapsed since prior dose
- Menveo
  - Primary vaccination for patients at increased risk of meningococcal disease:
    - Children initiating vaccination at 2 months of age: 4-dose series of 0.5 ml IM at 2, 4, 6, and 12 months of age
    - Children initiating vaccination at 7 to 23 months old: 2-dose series of 0.5 ml IM with second dose administered in 2nd year of life and at least 3 months after the first dose
    - Age 2 to 55 years: 0.5 ml IM single dose

Contraindications

Hypersensitivity to previous dose of meningococcal vaccine, diphtheria toxoid, or CRM_{197} containing vaccine

Essential Monitoring Parameters

- Syncope for 15 minutes following administration; in children, also monitor for fever, irritability, and drowsiness. Very rarely: high fever, febrile seizures, and persistent crying occur following vaccination.
- Monitor for shortness of breath, lip swelling, and rash or hives, which may occur rarely after administration of the vaccine

Counseling Points

- Injection-site reactions and fever are the most common adverse effects from the vaccine
- Report any chest tightness; wheezing; swelling of the lips, face, tongue, or throat; or seizures to the healthcare provider immediately

- Administered intramuscularly into the anterolateral thigh or upper deltoid

Key Points

- The minimum age for administration of Menveo is 2 months and for Menactra, it is 9 months.
- Combination vaccine available of Hib with *N. meningitides* serogroups C and Y as MenHibrix, which has a minimum administration age of 6 weeks
- This vaccine is usually administered as a single dose of Menactra or Menveo at age 11 through 12 years, with a booster dose at age 16 years
- Patients with high-risk conditions and at increased risk for meningococcal disease may need to be vaccinated earlier. A booster may need to be given every 5 years to patients who continue to be at increased risk. High-risk patients include:
  - People ≥ 2 months of age with anatomic or functional asplenia (including sickle cell disease), HIV infection, or persistent complement component deficiency (includes people with inherited or chronic deficiencies in C3, C5–9, properdin, factor D, factor H, or taking eculizumab)
  - People ≥ 2 months of age who travel to or reside in countries where meningococcal disease is hyperendemic or epidemic, especially if contact with the local population will be prolonged
  - Unvaccinated or incompletely vaccinated first-year college students living in residence halls
  - Military recruits
  - Microbiologists with occupational exposure
- Does not prevent *N. meningitidis* serogroup B infections

◉ Meningococcal Group B Vaccine

Brand Names

Bexsero, Trumenba

Generic Name

Meningococcal group B vaccine

Rx Only

Dosage Form

Injection

Usage

Active immunization for the prevention of invasive disease caused by *N. meningitidis* serogroup B

Pregnancy Category B

Dosing

- Bexsero: 2 doses of 0.5 ml IM at least 1 month apart
- Trumenba
  - 2-dose series: 0.5 ml IM at 0 and 6 months
  - 3-dose series: 0.5 ml IM at 1, 1 to 2, and 6 months

Contraindications

Hypersensitivity to previous dose of meningococcal vaccine

Essential Monitoring Parameters

- Syncope for 15 minutes following administration; in children, also monitor for fever, irritability, and drowsiness. Very rarely: high fever, febrile seizures, and persistent crying occur following vaccination.
- Monitor for shortness of breath, lip swelling, and rash or hives, which may occur rarely after administration of the vaccine
- Respiratory function in premature infants

Counseling Points

- Injection-site reactions and fever are the most common adverse effects from the vaccine
- Report any chest tightness; wheezing; swelling of the lips, face, tongue, or throat; or seizures to the healthcare provider immediately
- Administered intramuscularly into the anterolateral thigh or upper deltoid

Key Points

- Routine vaccination is recommended for children ≥ 10 years of age, adolescents, and unvaccinated adults with any of the following: Persistent complement component deficiencies (including patients who are taking eculizumab), anatomic or functional asplenia (including sickle cell disease), microbiologists routinely exposed to isolates of *N. meningitides*, or people identified to be at increased risk due to a serogroup B meningococcal disease outbreak
- The two meningococcal B vaccines (Bexsero and Trumenba) are not interchangeable and contain different immunologic targets. The same vaccine product must be used for all doses.
- Does not provide immunity against *N. meningitidis* serogroups A, C, W-135, or Y

◉ Rotavirus Vaccine

Brand Name

Rotarix, RotaTeq

Generic Name

Rotavirus Vaccine

Rx Only

Dosage Forms

Oral suspension, oral solution

Usage

- Rotarix: Provision of active immunity for the prevention of rotavirus gastroenteritis in infants 6 to 24 weeks of age caused by the serotypes G1, G3, G4, and G9 when administered as a 2-dose series

- RotaTeq: Provision of active immunity for the prevention of rotavirus gastroenteritis in infants 6 to 32 weeks of age caused by the serotypes G1, G2, G3, and G4 when administered as a 3-dose series

Pregnancy Category C

Dosing

- Rotarix: A total of two 1-ml doses or two 1.5-ml doses oral, the first dose given at 6 weeks of age, followed by the second dose ≥ 4 weeks later. Administer both doses by 24 weeks of age.
- RotaTeq: A total of three 2-ml doses oral, the first dose given at 6 to 12 weeks of age, followed by subsequent doses at 4 to 10 week intervals. Administer all doses by 32 weeks of age.

Adverse Reactions: Most Common

Irritability, fussiness, diarrhea, vomiting, otitis media

Adverse Reactions: Rare/Severe/Important

Anaphylaxis, angioedema, gastroenteritis, hematochezia, urticaria

Contraindications

History of uncorrected congenital malformation of the GI tract that would predispose the infant to intussusception, history of intussusception, severe combined immunodeficiency disease that would predispose the infant to gastroenteritis

Counseling Point

The most common adverse events associated with the rotavirus vaccine are irritability, diarrhea, and vomiting

Key Points

- The rotavirus vaccine is a live, attenuated, oral vaccine administered as a 2-dose series (Rotarix) or a 3-dose series (RotaTeq) beginning at 6 weeks of age
- The vaccination series should be completed with the same product whenever possible. If continuing with the same product will cause vaccination to be deferred, vaccination should be completed with the product available.
- Infants who have had rotavirus gastroenteritis before getting the full course of vaccine should still complete the vaccine series; initial infection provides only partial immunity
- Caution is recommended in infants with a history of GI disorders, acute mild GI illness, chronic diarrhea, and congenital abdominal disorders. The vaccine should not be administered to infants with acute moderate to severe gastroenteritis.
- Virus from live vaccines may be transmitted to nonvaccinated contacts; use with caution in the presence of immunocompromised family members

◉ Pneumococcal Conjugate Vaccine (13-valent)

Brand Name

Prevnar 13

Generic Name

Pneumococcal conjugate vaccine (13-valent)

Rx Only

Dosage Form

Injection

Usage

Provision of active immunity for the prevention of pneumococcal disease caused by the 13 serotypes contained in the vaccine

Pregnancy Category B

Dosing

- Adults: 0.5 ml IM as a single dose
- Infants and children: 0.5 ml IM for a total of four doses. Doses are typically administered at 2, 4, 6, and 12 to 15 months of age. The recommended dosing interval is 4 to 8 weeks.

Major Drug Interactions

Effect of Pneumococcal Conjugate Vaccine (13-Valent) on Other Drugs

The pneumococcal conjugate vaccine (13-valent) may diminish the effect of the influenza virus vaccine.

Essential Monitoring Parameters

Monitor for shortness of breath, lip swelling, chest pain, and syncope in the immediate period after administration of the vaccine

Counseling Point

The most common adverse effects from the vaccine include local injection-site reactions, fatigue, headache, and chills

Key Points

- Pneumococcal 13-valent conjugate vaccine is the successor to the previously marketed pneumococcal 7-valent conjugate vaccine. Prevnar 13 contains an additional six serotypes of *S. pneumoniae*, compared with the seven serotypes provided in the original Prevnar formulation.
- The pneumococcal 13-valent conjugate vaccine should not be confused with the pneumococcal 7-valent vaccine or the pneumococcal polysaccharide vaccine (23-valent). The pneumococcal 13-valent vaccine is indicated as a primary series in infants and children < 2 years of age, for children and

adults 2 to 64 years of age with certain health conditions, and all adults ≥ 65 years of age.
- It is typical for elderly patients to receive both polysaccharide and conjugate pneumococcal vaccines. In 2017, the recommended administration schedule is to give pneumococcal conjugate vaccine at age 65, then pneumococcal polysaccharide vaccine 12 months later.

Pneumococcal Polysaccharide Vaccine

Brand Name
Pneumovax 23

Generic Name
Pneumococcal polysaccharide vaccine

Rx Only

Dosage Form
Injection

Usage
Provision of active immunity for the prevention of pneumococcal diseases caused by the 23 serotypes contained in the vaccine

Pregnancy Category C

Dosing
0.5 ml IM or SUB-Q

Major Drug Interactions
Pneumococcal Polysaccharide Vaccine's Effect on Other Drugs

Zoster vaccine: Separate administration by 4 weeks to prevent reduced immune response to the zoster vaccine

Counseling Point
Tell your healthcare provider immediately if you experience wheezing, difficulty breathing, or rash or hives

Key Points
- The following populations should receive the pneumococcal polysaccharide vaccine:
  - All adults ≥ 65 years of age
  - Children and adults 2 to 64 years of age who:
    - Have a long-term health problem (e.g., heart disease, lung disease, diabetes)
    - Are immunocompromised (e.g., malignancies such as leukemia or lymphoma, HIV infection, or damaged spleen)
    - Are taking immunosuppressive therapy (e.g., long-term steroids)
  - Adults 19 to 64 years of age who smoke or have chronic heart disease or asthma
- Not approved for children < 2 years of age
- Should not be confused with the pneumococcal conjugate vaccine, which is often given to children < 2 years of age and does not provide immunity to as many serotypes as the pneumococcal polysaccharide vaccine
- It is typical for elderly patients to receive both polysaccharide and conjugate pneumococcal vaccines. In 2017, the recommended administration schedule is to give pneumococcal conjugate vaccine at age 65, then pneumococcal polysaccharide vaccine 12 months later.

Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine (Tdap)

Brand Name
Adacel, Boostrix

Generic Name
Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine

Rx Only

Dosage Form
Injection

Usage
The provision of active immunity for the prevention of disease against tetanus, diphtheria, and pertussis in adults for whom their vaccine status is not known

Pregnancy Category B/C (Manufacturer Specific)

Dosing
- 0.5 ml IM as a single dose
  - Children 7 to 10 years of age who did not complete a full primary DTaP series should receive a single dose of Tdap
  - Adolescents 11 to 18 years of age who have completed their primary vaccination series with DTaP should receive a single dose of Tdap as a booster injection

Contraindications
- Encephalopathy within 7 days of administration of a previous pertussis antigen-containing vaccine that is not attributable to another identifiable cause is a contraindication to administration of the vaccine
- Progressive or unstable neurologic conditions are reasons to defer vaccination with the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine

Essential Monitoring Parameters
- Monitor for hypersensitivity or anaphylaxis reactions, including rash, hives, dyspnea, lip swelling, and chest tightness
- Monitor for syncope 15 minutes following administration of the vaccine

Counseling Point

Injection-site reactions, headache, and fatigue are the most common side effects of the vaccine

Key Points

- Adacel is formulated with the same antigens found in Daptacel, but with reduced quantities of tetanus and pertussis. Use in the primary series immunization has not been studied.
- Boostrix is formulated with the same antigens found in Infanrix, but in reduced quantities. Use in the primary series immunization has not been studied.
- Tdap can be administered regardless of the interval between the last tetanus or diphtheria toxoid–containing vaccine. It is currently recommended for a single dose only.
- Adacel or Boostrix may be administered as an alternative to the Td vaccine when a tetanus-toxoid–containing vaccine is needed for wound management, if it has been ≥ 5 years since the last dose
- A single dose of Tdap is recommended during each pregnancy during 27 and 36 weeks' gestation, as well as for healthcare workers with direct patient contact who have not previously received Tdap
- Administer IM in the deltoid muscle of the upper arm
- Caution is recommended in patients with a history of seizure disorder or progressive neurologic disorder

⦿ Varicella Virus Vaccine

Brand Names

Varivax

Generic Name

Varicella virus vaccine (live)

Rx Only

Dosage Form

Injection

Usage

Active immunization for the prevention of varicella

Pregnancy

Do not administer to pregnant females and pregnancy should be avoided for 3 months following vaccination

Dosing

Varicella immunization:

- Children 12 months to 12 years of age: 2 doses of 0.5 ml SUB-Q separated by at least 3 months
- ≥ 13 years of age and adults: 2 doses of 0.5 ml SUB-Q separated by at least 4 weeks
- Varicella postexposure prophylaxis in healthy, previously unvaccinated individuals (children ≥ 12 months, adolescents, and adults): 0.5 ml SUB-Q administered within 3 to 5 days of exposure

Adverse Reactions: Rare/Severe/Important

Anaphylactic or anaphylactoid reactions (hives and angioedema, difficulty breathing, hypotension, and shock), varicella-like rash, syncope

Major Drug Interactions

Drugs Affecting Varicella Virus Vaccine

Antiviral drugs (acyclovir, famciclovir, valacyclovir): Medications active against herpes virus family may interfere with the varicella vaccine. Avoid vaccine in patients who have received these antivirals within 24 hours and avoid using the antiviral drugs for 14 days after varicella vaccination.

Varicella Virus Vaccine's Effect on Other Drugs

- Salicylates: Avoid salicylates in children and adolescents 12 months through 17 years of age for 6 weeks after vaccination because varicella may increase the risk of developing Reye's syndrome
- Tuberculin tests: The varicella vaccine may diminish the diagnostic effect of the tuberculin test. A PPD test should not be scheduled for at least 4 to 6 weeks following the administration of the vaccine.

Contraindications

History of severe allergic reaction to neomycin, gelatin, or previous dose of varicella vaccine; immunosuppressed or immunodeficient individuals, including individuals with leukemia, lymphomas, or other malignant neoplasms affecting the bone marrow or lymphatic systems; persons with AIDs or other clinical manifestations of HIV; those receiving immunosuppressive therapy (including immunosuppressive doses of corticosteroids); primary or acquired immunodeficiency states; any febrile illness or active infection, including untreated tuberculosis; pregnancy.

Essential Monitoring Parameters

- Syncope for 15 minutes following administration
- Fever, rash, seizures
- Monitor for shortness of breath, lip swelling, and rash or hives, which may occur rarely after administration of the vaccine

Counseling Points

- Injection-site reactions and fever are the most common adverse effects from the vaccine
- Report any chest tightness; wheezing; swelling of the lips, face, tongue, or throat; or seizures to the healthcare provider immediately
- Vaccinated individuals should not have close association with susceptible high-risk individuals for 6 weeks following vaccination. High-risk individuals include immunocompromised people, pregnant women without evidence of immunity, newborns of mothers without evidence of immunity, and all infants born < 28 weeks' gestation.

- Tell your doctor if you are taking medications to suppress the immune system. These medications may decrease the effectiveness of the vaccine.
- You should not receive this vaccine if you are pregnant or plan to get pregnant within the next three months

Key Points

- This is a live, attenuated vaccine
- Do not give to children younger than 12 months of age
- Administered as a 2–dose series at ages 12 to 15 months and 4 to 6 years of age. Second dose can be administered before 4 years of age provided that at least 3 months have passed since first dose.
- Recommended for the following, who don't have evidence of immunity:
  - Adults with close contact with people at high risk for serious complications (healthcare personnel and household contacts of immunocompromised people)
  - Adults who live or work in an environment in which transmission of varicella zoster virus is likely (teachers, childcare workers, and residents and staff in institutional settings)
  - Adults who live or work in environments in which varicella transmission has been reported (college students, residents and staff members of correctional institutions, and military personnel)
  - Nonpregnant women of childbearing age
  - Adolescents and adults living in households with children
  - International travelers
- Evidence of immunity to varicella in adults is: U.S.-born before 1980 (for pregnant women and healthcare personnel, U.S.-born before 1980 is not considered evidence of immunity); documentation of 2 doses of vaccine at least 4 weeks apart; history of varicella or herpes zoster diagnosis or verification of varicella or herpes zoster disease by a healthcare provider; or laboratory evidence of immunity or disease
- Contraindicated in patients who are immunosuppressed, have febrile illness or active infection, and those who are pregnant
- Also available as varicella vaccine in combination with MMR vaccine (ProQuad)

⦿ Zoster Vaccine

Brand Name

Zostavax

Generic Name

Zoster vaccine

Rx Only

Dosage Form

Injection

Usage

Prevention of herpes zoster (shingles) in patients ≥ 50 years of age

Pregnancy Category

Use during pregnancy is contraindicated

Dosing

Single 0.65 ml dose SUB-Q

Adverse Reactions: Most Common

Injection-site reactions (pain, redness, swelling), headache

Major Drug Interactions

Drugs Affecting the Zoster Vaccine

- Pneumococcal polysaccharide vaccine: Separate administration by 4 weeks to prevent reduced immune response to the zoster vaccine
- Acyclovir, famciclovir, valacyclovir: Discontinue these medications at least 24 hours before administration of zoster vaccine, if possible

Contraindications

History of anaphylactic/anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine; immunosuppression or immunodeficiency; pregnancy

Counseling Points

- Injection-site reactions and headache are common adverse reactions
- Tell your doctor if you are taking medications to suppress the immune system. These medications may decrease the effectiveness of the zoster vaccine.
- Do not receive this vaccine if you are pregnant or plan to get pregnant within the next 3 months

Key Points

- The zoster vaccine is a live attenuated vaccine
- The zoster vaccine is a one-time vaccination
- The zoster vaccine is not a substitute for the varicella vaccine and should not be used in patients < 50 years of age. The varicella vaccine is indicated for the prevention of chickenpox. Its dosing and composition are distinct from the zoster vaccine.
- Although the FDA approved zoster vaccine for use in those ≥ 50 years of age, the Centers for Disease Control and Prevention recommends use in people ≥ 60 years of age
- Even if patients have had shingles previously, they can still receive the shingles vaccine to help prevent future occurrences of the disease
- The zoster vaccine is not recommended for persons of any age who have received the varicella vaccine

IMMUNOSUPPRESSANT AGENTS, CALCINEURIN INHIBITORS

Introduction

Calcineurin inhibitors are the backbone of organ transplant immunosuppression. They are used in combination with other immunosuppressant agents to prevent organ rejection after transplant. They can also be used for the treatment of other immunologic conditions but usually not as first-line therapy. These medications require therapeutic drug monitoring of serum concentrations and have many drug interactions.

Mechanism of Action for the Drug Class

Inhibit interleukin-2 production, and subsequently T cell differentiation and proliferation, thus preventing allograft rejection. Cyclosporine and tacrolimus block T cell production by binding to the cytoplasmic proteins, cyclophilin and FK-binding protein, respectively. These drug-protein complexes inhibit the action of calcineurin, an enzyme that is responsible for transcription of several cytokines, including interleukin-2. Interleukin-2 is a T-cell growth factor that is ultimately responsible for T lymphocyte synthesis.

Members of the Drug Class

In this section: Cyclosporine, tacrolimus
Other: Pimecrolimus

◉ Cyclosporine

Brand Names

Gengraf, Neoral, Restasis, Sandimmune

Generic Name

Cyclosporine

Rx Only

Dosage Forms

Capsule, oral solution, injection, eye drops

Usage

Prevention of organ transplant rejection, prevention and treatment of graft-versus-host disease, rheumatoid arthritis, psoriasis, severe ulcerative colitis; increase tear production (Restasis only)

Pregnancy Category C

Dosing

- Prevention of organ transplant rejection:
  - Oral: 7–15 mg/kg in 2 divided doses, depending on type of transplant. Subsequent doses are adjusted based on serum concentrations.
  - IV: One-third of the oral dose infused over 2 to 6 hours
- Rheumatoid arthritis:
  - 2.5 mg/kg per day in 2 divided doses; dose is titrated based on response
  - Maximum dose: 4 mg/kg per day
- Psoriasis:
  - 2.5 mg/kg per day in 2 divided doses; dose is titrated based on response
  - Maximum dose: 4 mg/kg per day
- Severe ulcerative colitis:
  - Oral: 5–10 mg/kg per day in 2 divided doses
  - IV: 2–4 mg/kg per day infused continuously over 24 hours
- Increase tear production: 1 drop in each eye every 12 hours
- Renal dosage adjustment: Adjust dose to maintain lower cyclosporine blood trough concentrations

Pharmacokinetic Monitoring

Monitor trough serum levels. Therapeutic range is based on the organ transplanted, time after transplant, and organ function. Typical range is 25–200 ng/ml.

Adverse Reactions: Most Common

Oral, IV: Edema, hirsutism, gingival hyperplasia, headache, tremor, increased triglycerides.
Ophthalmic: Burning, stinging

Adverse Reactions: Rare/Severe/Important

Oral, IV: Hypertension, nephrotoxicity, hyperkalemia, hypomagnesemia, hyperuricemia, hepatotoxicity, coma, encephalopathy, leukoencephalopathy, seizure, hemolytic uremic syndrome, infectious disease, lymphoma

Major Drug Interactions

Drugs Affecting Cyclosporine

- CYP3A4 inducers (i.e., phenytoin, phenobarbital, carbamazepine, rifampin, nevirapine, St. John's wort): Decrease blood concentrations
- CYP3A4 inhibitors (i.e., azole antifungals, amiodarone, macrolide antibiotics, diltiazem, verapamil, ritonavir, grapefruit juice): Increase toxicity
- Allopurinol: Increases toxicity
- Vancomycin, aminoglycosides, ACE inhibitors, colchicine, NSAIDs: May potentiate renal dysfunction
- ACE inhibitors, potassium–sparing diuretics: May enhance hyperkalemic effect

Cyclosporine's Effects on Other Drugs

- HMG-CoA reductase inhibitors: Increases HMG-CoA reductase inhibitor concentrations, placing patients at an increased risk of rhabdomyolysis
- Digoxin: Increases levels
- Dabigatran: Increases concentrations of dabigatran's active metabolites

Contraindications

- IV formulation contraindicated in patients with hypersensitivity to polyoxyethylated castor oil
- Rheumatoid arthritis and psoriasis: Abnormal renal function, uncontrolled hypertension, malignancies
- Psoriasis: Concomitant treatment with PUVA or UVB therapy, methotrexate, other immunosuppressive agents, coal tar, or radiation therapy
- Ophthalmic cyclosporine is contraindicated in patients with ocular infections

Essential Monitoring Parameters

Trough serum levels, renal function, potassium, magnesium, liver function, blood pressure, lipids, uric acid, infection, hypersensitivity reactions (IV cyclosporine)

Counseling Points

- Take prescribed dose at the same time each day with meals
- When administering the solution, mix with water or orange juice in a glass, not plastic, container, then stir and drink all at once
- Avoid grapefruits and grapefruit juice, which can affect the metabolism of cyclosporine
- Avoid live vaccines while on therapy or within 3 months of discontinuing therapy
- Frequent laboratory monitoring will be needed

Key Points

- **Black Box Warnings:**
  - May cause hypertension; risk is increased with increasing doses and duration. There is an increased risk of infection, as well as lymphomas and other malignancies with use. Cyclosporine may cause renal impairment, including structural kidney damage; the risk is increased with increasing doses and duration.
- Cyclosporine modified (Neoral, Gengraf) and nonmodified (Sandimmune) products are not bioequivalent and not interchangeable
- Bioavailability of nonmodified (Sandimmune) oral solution is 30% of the IV solution
- Nonmodified (Sandimmune) capsules and oral solution have decreased bioavailability compared with modified (Neoral) formulations. Cyclosporine blood trough concentrations should be monitored frequently (every 4 to 7 days until stable blood trough levels are achieved) when switching among products.
- Cyclosporine dose adjustments should be made in small increments (about a 25% change at any one time)

Tacrolimus

Brand Names

Prograf, Astagraf XL, Envarsus XR, Hecoria, Protopic

Generic Name

Tacrolimus

Rx Only

Dosage Forms

Capsule, extended-release capsule, extended-release tablet, ointment, injection

Usage

Prevention of organ transplant rejection, prevention, and treatment of graft-versus-host disease, moderate to severe atopic dermatitis

Pregnancy Category C

Dosing

- Prevention of organ transplant rejection:
  - Oral (immediate release): 0.075–0.2 mg/kg per day in 2 divided doses, depending on type of transplant
  - Oral (extended release): 0.1–0.2 mg/kg/day. Titrate to target trough concentrations.
  - IV: 0.01 to 0.05 mg/kg per day as a continuous infusion
  - Renal dosage adjustment for oral and IV: Adjust dose to maintain lower tacrolimus blood trough concentrations
  - Hepatic dosage adjustment for oral and IV: In cases of severe hepatic impairment, lower doses may be required. Monitor tacrolimus blood trough concentrations and adjust dose based on levels.
- Atopic dermatitis: Apply thin layer of topical formulation to affected area twice daily

Pharmacokinetic Monitoring

Trough serum levels should be monitored. Therapeutic range is based on the organ transplanted, time after transplant, and organ function. Typical range is 5–20 ng/ml.

Adverse Reactions: Most Common

Oral, IV: Alopecia, pruritus, rash, constipation, diarrhea, nausea, vomiting, anemia, leukocytosis or leukopenia, thrombocytopenia, headache, insomnia, paresthesia, tremor. Topical: skin burning, pruritus, erythema, paresthesia

Adverse Reactions: Rare/Severe/Important

Hypertension, prolonged QT interval, diabetes mellitus, hypomagnesemia, hyperkalemia, anaphylaxis, infectious disease, lymphoma, seizure, leukoencephalopathy, nephrotoxicity, hepatotoxicity

Major Drug Interactions

Drugs Affecting Tacrolimus

- Alcohol: May increase the absorption of tacrolimus, as the speed of release of tacrolimus may be increased from extended-release tablets
- Potent CYP3A4 inhibitors (i.e., azole antifungals, amiodarone, macrolide antibiotics, diltiazem, verapamil, ritonavir, grapefruit juice): Increase toxicity
- Potent CYP3A4 inducers (i.e., phenytoin, phenobarbital, carbamazepine, rifampin, nevirapine, St. John's wort): Decrease concentration

- QT-prolonging drugs (i.e., haloperidol, methadone, amiodarone, sotalol, erythromycin, clarithromycin): Increase risk of QT prolongation
- Vancomycin, aminoglycosides, ACE inhibitors, colchicine, NSAIDs: May potentiate renal dysfunction
- Proton pump inhibitors: Increase concentration
- ACE inhibitors, potassium-sparing diuretics: May enhance hyperkalemic effect

Tacrolimus' Effect on Other Drugs

- Dabigatran: Increases concentrations of dabigatran's active metabolites

Contraindications

IV formulation contraindicated in patients with hypersensitivity to polyoxyethylated castor oil

Essential Monitoring Parameters

Trough serum levels, renal function, potassium, magnesium, liver function, blood pressure, blood glucose

Counseling Points

- Take prescribed dose at the same time each day. Tacrolimus may be taken with or without food as long as you are consistent.
- Avoid grapefruits and grapefruit juice, which can affect the metabolism of tacrolimus
- Avoid live vaccines while on therapy or within 3 months of discontinuing therapy
- Frequent laboratory monitoring will be needed

Key Points

- **Black Box Warnings:**
  - There is an increased risk of development of lymphoma and other malignancies, particularly of the skin, due to immunosuppression. There is increased susceptibility to bacterial, viral, fungal, and protozoal infections in patients receiving tacrolimus, including opportunistic infections.
- Dose adjustments are necessary in patients with renal and hepatic insufficiency. These patients should be dosed on the lower end of the typical dosing range and trough levels should be monitored closely. A typical trough range for tacrolimus is 5–20 ng/ml.
- Tacrolimus can cause serious side effects, including hypertension, hyperkalemia, hypomagnesemia, hyperglycemia, nephrotoxicity, hepatotoxicity, and prolonged QT interval. Patients should be monitored closely for these adverse effects by assessing BP, electrolytes, BUN, SCr, LFTs and the QT interval.
- Tacrolimus is a major CYP3A4 substrate. Therefore, is not recommended to use tacrolimus with potent CYP3A4 inducers (i.e., phenytoin, phenobarbital, rifampin, carbamazepine) or inhibitors (i.e., ketoconazole, itraconazole, amiodarone, clarithromycin, erythromycin, grapefruit juice).

IMMUNOSUPPRESSANT AGENTS, IMPDH INHIBITORS

Introduction

IMPDH inhibitors are used concomitantly with other immunosuppressant medications, such as steroids and a calcineurin inhibitor, to prevent organ transplant rejection. Like the calcineurin inhibitors, they can also be used to treat other immunologic conditions. Unlike calcineurin inhibitors, trough levels are not monitored.

Mechanism of Action for the Drug Class

IMPDH inhibitors inhibit inosine monophosphate dehydrogenase (IMPDH), an enzyme that is essential for T- and B-cell proliferation. IMPDH catalyzes the rate-limiting step in purine nucleotide synthesis, which is essential for lymphocyte production. Mycophenolic acid targets IMPDH II most specifically, which is expressed only in T and B lymphocytes, compared with IMPDH I, which is expressed by all cells in the body.

Members of the Drug Class

In this section: Mycophenolic acid

◉ Mycophenolic Acid

Brand Names

CellCept, Myfortic

Generic Names

Mycophenolic acid, mycophenolate mofetil

Rx Only

Dosage Forms

Capsule, tablet, delayed-release tablet, oral suspension, injection

Usage

Prevention of organ transplant rejection, moderate to severe psoriasis, prevention and treatment of graft-versus-host disease, lupus nephritis, myasthenia gravis, refractory autoimmune hepatitis

Pregnancy Category D

Dosing

Prevention of organ transplant rejection:

- Oral:
  - CellCept: 2–3 g per day in 2 divided doses
  - Myfortic: 1440 mg per day in 2 divided doses
- IV: CellCept 2–3 g per day in 2 divided doses

Adverse Reactions: Most Common

Edema, hyper- or hypotension, headache, insomnia, leukopenia or leukocytosis, hyperglycemia, anemia, thrombocytopenia, hypercholesterolemia, weakness, tremor, nausea, vomiting, diarrhea, constipation, hypomagnesemia, hyper- or hypokalemia

Adverse Reactions: Rare/Severe/Important

Infectious disease, lymphoma, neutropenia, anemia, nephrotoxicity, hepatotoxicity, gastrointestinal ulcers/bleeding

Major Drug Interactions

Drugs Affecting Mycophenolic Acid

- Antacids, cholestyramine, sevelamer: Decrease absorption
- Acyclovir/ valacyclovir: Increases concentrations
- Cyclosporine: Decreases concentrations
- Probenecid: Increases concentrations
- Proton pump inhibitors: Decrease concentrations
- Rifamycins: Decrease concentrations

Mycophenolic Acid's Effect on Other Drugs

- Contraceptives: Decreases concentration of contraceptives (estrogens and progestins)

Contraindication

IV Formulation contraindicated in patients with hypersensitivity to polysorbate 80

Essential Monitoring Parameters

Blood pressure, electrolytes, renal function, liver function, complete blood count

Counseling Points

- Women of childbearing age must have a negative urine or serum pregnancy test within 1 week prior to starting therapy
- Two forms of contraceptives should be used 4 weeks prior to starting mycophenolic acid, unless abstinence is the chosen method. Continue contraceptives for 6 weeks after stopping therapy.
- Breastfeeding is not recommended during therapy or for 6 weeks after completing therapy
- Oral dosage forms should be taken on an empty stomach to avoid variability in absorption
- Delayed-release tablets (Myfortic) should not be crushed, cut, or chewed
- Avoid live vaccines while on therapy or within 3 months of discontinuing therapy

Key Points

- **Black Box Warnings:**
  - There is a risk for bacterial, viral, fungal, and protozoal infections, including opportunistic infections, while receiving mycophenolic acid. The risk of developing lymphoma and skin malignancy is increased. Mycophenolic acid is associated with an increased risk of congenital malformations and females of reproductive potential must be counseled about pregnancy prevention and planning.
- CellCept and Myfortic dosage forms are not interchangeable due to differences in absorption
- Because mycophenolic acid commonly causes leukopenia, it may mask leukocytosis in patients with infections

TUMOR NECROSIS FACTOR INHIBITORS

Introduction

Tumor necrosis factor (TNF) inhibitors are genetically engineered protein molecules that block the proinflammatory cytokine TNF-alpha. These medications are used in the treatment of autoimmune disorders, such as rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, plaque psoriasis, and psoriatic arthritis, when other options fail to achieve adequate response. These agents are expensive and have many adverse effects.

A note on biosimilars: Since these biologic drugs are made from living organisms via biotechnology, if another manufacturer produces the drug, it is referred to as a biosimilar. A biosimilar product is a biologic product that is approved based on demonstrating that it is highly similar to an FDA-approved biologic product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically

inactive components are allowable in biosimilar products. A biosimilar product can be an interchangeable biologic product if it meets additional standards for interchangeability and can then be substituted for the reference product by a pharmacist without the intervention of the healthcare provider who prescribed the reference product. The specific generic name has a core drug substance name and an FDA-designated, four-letter suffix that is unique for each product (i.e., adalimumab-atto, etanercept-szzs, and infliximab-dyyb). This naming process is designed to help prevent inadvertent substitution (which could lead to medication errors) of biologic products that are not determined to be interchangeable by the FDA and to support safety monitoring of all biologic products.

Mechanism of Action for the Drug Class

TNF blockers bind TNF and inhibit its interaction with TNF receptors. This prevents the activation of the signaling pathway involved in the release of inflammatory mediators that are involved in the inflammatory processes.

Key Points for the Drug Class

- **Black Box Warnings:**
  - TNF-alpha inhibitors increase the risk of developing serious infections that may lead to hospitalization or death. They are also associated with lymphoma and other malignancies.
- Patients should be evaluated for latent tuberculosis infection with a tuberculin skin test before therapy
- Rare reactivation of hepatitis B has occurred while receiving these agents. Evaluate before initiation and during treatment.
- Use caution in patients with chronic infections. If a patient develops an acute serious infection or sepsis, the medication should be discontinued.

Members of the Drug Class

In this section: Etanercept, infliximab, adalimumab, certolizumab pegol, golimumab

⦿ Etanercept

Brand Name

Enbrel, Erelzi (biosimilar)

Generic Name

Etanercept, etanercept-szzs

Rx Only

Dosage Form

Injection

Usage

Treatment of moderate to severe active RA, moderate to severe active polyarticular JIA, psoriatic arthritis, active *ankylosing spondylitis, moderate to severe chronic plaque psoriasis hidradenitis suppurativa*

Pregnancy Category B

Dosing

- Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis:
  - Etanercept: 25 mg SUB-Q twice weekly *or* 50 mg SUB-Q once weekly
  - Etanercept-szzs: 50 mg SUB-Q once weekly
- Plaque psoriasis (etanercept and etanercept-szzs): 50 mg SUB-Q twice weekly for 3 months, then 50 mg SUB-Q once weekly

Adverse Reactions: Most Common

Injection-site reaction, headache, rhinitis, upper respiratory infection

Adverse Reactions: Rare/Severe/Important

Anaphylaxis, autoimmune diseases (lupus-like syndrome, autoimmune hepatitis), heart failure, malignancies (lymphoma, others), optic neuritis, multiple sclerosis, pancytopenia, anemia, serious infections (*Legionella* pneumonia; listeriosis; tuberculosis; invasive fungal, bacterial, viral, and opportunistic infections), erythema multiforme, Stevens-Johnson syndrome

Major Drug Interactions

Etanercept's Effect on Other Drugs

- Disease-modifying antirheumatic drugs (DMARDs; abatacept, anakinra, natalizumab) and other concomitant immunosuppressive agents: Increase risk of infection, toxicities, and immunosuppression
- Vaccines: Efficacy of inactivated vaccines may be reduced, increase risk of developing vaccinial infections with live vaccines

Contraindications

Patients with active infections

Essential Monitoring Parameters

Screen for latent TB and hepatitis B prior to initiating therapy; during therapy, monitor CBC, signs/symptoms of heart failure, infection, and malignancy

Counseling Points

- Stop medication and contact your healthcare provider immediately if you experience stomach pain or cramping, unusual bruising or bleeding, persistent fever, rash, night sweats, significant weight loss, muscle weakness, and/or signs of respiratory infections
- Avoid receiving immunizations during therapy and for at least 3 months after therapy with TNF inhibitors
- Rotate injection sites—new injections should be given at least 1 inch from an old site
- Medication should be stored in the refrigerator

Key Points

- Use caution in patients with heart failure because exacerbations may occur
- Has biosimilar product that is not interchangeable

Infliximab

Brand Name

Remicade, Inflectra (biosimilar)

Generic Name

Infliximab, infliximab-dyyb

Rx Only

Dosage Form

Injection

Usage

Treatment of moderate to severe RA, moderate to severe Crohn's disease, moderate to severe ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, hidradenitis suppurativa, JIA

Pregnancy Category B

Dosing

- Crohn's disease and ulcerative colitis: 5 mg/kg IV at 0, 2, and 6 weeks, followed by 5 mg/kg every 8 weeks thereafter
- RA (in combination with methotrexate): 3 mg/kg IV at 0, 2, and 6 weeks, then every 8 weeks thereafter

Adverse Reactions: Most Common

Abdominal pain, increased ALT, headache, upper respiratory infection

Adverse Reactions: Rare/Severe/Important

Infusion reactions, autoimmune diseases (positive antinuclear antibody titers, lupus-like syndrome), hepatitis, heart failure, malignancies (lymphoma, others), optic neuritis, multiple sclerosis, pancytopenia, leukopenia, serious infections (*Legionella* pneumonia; listeriosis; tuberculosis; invasive fungal, bacterial, viral, and opportunistic infections), erythema multiforme, Stevens-Johnson syndrome

Major Drug Interactions

Infliximab's Effect on Other Drugs

- Disease-modifying antirheumatic drugs (DMARDs; abatacept, anakinra, natalizumab) and other concomitant immunosuppressive agents: Increase risk of infection, toxicities, and immunosuppression
- Vaccines: Efficacy of inactivated vaccines may be reduced; increase risk of developing vaccinial infections with live vaccines

Contraindications

Previous hypersensitivity to murine proteins, doses > 5 mg/kg in moderate to severe heart failure

Essential Monitoring Parameters

Screen for latent TB and hepatitis B prior to initiating therapy; during therapy, monitor CBC, LFTs, signs/symptoms of heart failure, infection, and malignancy

Counseling Points

- Stop medication and contact your healthcare provider immediately if you experience stomach pain or cramping, unusual bruising or bleeding, persistent fever, rash, night sweats, significant weight loss, muscle weakness, and/or signs of respiratory infections
- Avoid receiving immunizations during therapy and for at least 3 months after therapy with TNF inhibitors

Key Points

- High doses contraindicated in patients with moderate to severe heart failure.
- Has biosimilar product that is not interchangeable
- Must be given intravenously

Adalimumab

Brand Name

Humira, Amjevita (biosimilar)

Generic Name

Adalimumab, adalimumab-atto

Rx Only

Dosage Form

Injection

Usage

Treatment of moderate to severe RA, moderate to severe Crohn's disease, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, severe JIA, ulcerative colitis

Pregnancy Category B

Dosing

- RA: 40 mg SUB-Q once every other week
- Crohn's disease: 160 mg SUB-Q (given as four injections on day 1 or as two injections per day over 2 consecutive days), then 80 mg SUB-Q 2 weeks later. Maintenance: 40 mg SUB-Q every other week beginning on day 29.

Adverse Reactions: Most Common

Injection-site reaction, headache, upper respiratory infection, increased CPK

Adverse Reactions: Rare/Severe/Important

Anaphylaxis, autoimmune diseases (positive antinuclear antibody titers, lupus-like syndrome), hepatitis, heart failure, malignancies (lymphoma, others), optic neuritis, multiple sclerosis, pancytopenia, aplastic anemia, serious infections (*Legionella* pneumonia, listeriosis, tuberculosis,

invasive fungal, bacterial, viral, and opportunistic infections), erythema multiforme, Stevens-Johnson syndrome

Major Drug Interactions

Adalimumab's Effect on Other Drugs

- Disease-modifying antirheumatic drugs (DMARDs; abatacept, anakinra, natalizumab) and other concomitant immunosuppressive agents: Increase risk of infection, toxicities, and immunosuppression
- Vaccines: Efficacy of inactivated vaccines may be reduced, increase risk of developing vaccinial infections with live vaccines

Contraindications

None

Essential Monitoring Parameters

Screen for latent TB and hepatitis B prior to initiating therapy; during therapy, monitor CBC, signs/symptoms of heart failure, infection, and malignancy

Counseling Points

- Stop medication and contact your healthcare provider immediately if you experience stomach pain or cramping, unusual bruising or bleeding, persistent fever, rash, night sweats, significant weight loss, muscle weakness, and/or signs of respiratory infection
- Avoid receiving immunizations during therapy and for at least 3 months after therapy with TNF inhibitors

Key Points

- High doses contraindicated in patients with moderate to severe heart failure
- Has biosimilar product that is not interchangeable

◉ Certolizumab Pegol

Brand Name

Cimzia

Generic Name

Certolizumab pegol

Rx Only

Dosage Form

Injection

Usage

Treatment of moderate to severe RA, moderate to severe Crohn's disease, psoriatic arthritis, ankylosing spondylitis

Pregnancy Category

Limited data from the ongoing pregnancy registry are not sufficient to inform a risk of major birth defects or other adverse pregnancy outcomes. Adverse effects have not been observed in animal reproduction studies. There is a pregnancy exposure registry.

Dosing

- Initial dose for all indications: 400 mg SUB-Q, repeated at 2 and 4 weeks after the initial dose
- Maintenance dose:
  - RA, psoriatic arthritis, ankylosing spondylitis: 200 mg SUB-Q every 2 weeks or 400 mg SUB-Q every 4 weeks
  - Crohn's disease: 400 mg SUB-Q every 4 weeks

Adverse Reactions: Most Common

Upper respiratory infection, nausea, rash, injection-site reaction

Adverse Reactions: Rare/Severe/Important

Autoimmune diseases (lupus-like syndrome), demyelinating CNS disease (optic neuritis, seizures, peripheral neuropathy, MS, Guillain–Barré syndrome), pancytopenia, reactivation of hepatitis B, anaphylaxis, serious infections (*Legionella* pneumonia; listeriosis; tuberculosis; invasive fungal, bacterial, viral, and opportunistic infections) malignancies (lymphoma, others, worsening/new onset heart failure

Major Drug Interactions

Certolizumab's Effect on Other Drugs

- Disease-modifying antirheumatic drugs (DMARDs; abatacept, anakinra, natalizumab) and other concomitant immunosuppressive agents: Increase risk of infection, toxicities, and immunosuppression
- Vaccines: Efficacy of inactivated vaccines may be reduced; increase risk of developing vaccinial infections with live vaccines

Contraindications

None

Essential Monitoring Parameters

Screen for latent TB and hepatitis B prior to initiating therapy; during therapy, monitor CBC, signs/symptoms of heart failure, infection, and malignancy

Counseling Points

- Stop medication and contact your healthcare provider immediately if you experience stomach pain or cramping, unusual bruising or bleeding, persistent fever, rash, night sweats, significant weight loss, muscle weakness, and/or signs of respiratory infections
- Avoid receiving immunizations during therapy and for at least 3 months after therapy with TNF inhibitors

Key Point

May interfere with certain coagulation assays and cause erroneously elevated aPTT in patients without coagulation abnormalities

Golimumab

Brand Name
Simponi

Generic Name
Golimumab

Rx Only

Dosage Form
Injection

Usage
Treatment of moderate to severe RA, moderate to severe ulcerative colitis, psoriatic arthritis, ankylosing spondylitis

Pregnancy Category: B

Dosing
- RA, psoriatic arthritis, ankylosing spondylitis: 50 mg SUB-Q once a month
- Can also be given IV for RA: 2 mg/kg at weeks 0, 4, then every 8 weeks thereafter
- Ulcerative colitis: 200 mg SUB-Q initially, then 100 mg SUB-Q week 2, then 100 mg SUB-Q every 4 weeks

Adverse Reactions: Most Common
Infection, injection-site reaction

Adverse Reactions: Rare/Severe/Important
Autoimmune diseases (lupus-like syndrome), demyelinating CNS disease (optic neuritis, seizures, peripheral neuropathy, MS, Guillain–Barré syndrome), pancytopenia, reactivation of hepatitis B, anaphylaxis, serious infections (*Legionella* pneumonia; listeriosis; tuberculosis; invasive fungal, bacterial, viral, and opportunistic infections), malignancies (lymphoma, others), worsening/new onset heart failure

Major Drug Interactions
Golimumab's Effect on Other Drugs
- Disease-modifying antirheumatic drugs (DMARDs; abatacept, anakinra, natalizumab) and other concomitant immunosuppressive agents: Increase risk of infection, toxicities, and immunosuppression
- Vaccines: Efficacy of inactivated vaccines may be reduced; increase risk of developing vaccinial infections with live vaccines

Contraindications
None

Essential Monitoring Parameters
Screen for latent TB and hepatitis B prior to initiating therapy; during therapy, monitor CBC, signs/symptoms of heart failure, infection, and malignancy

Counseling Points
- Stop medication and contact your healthcare provider immediately if you experience stomach pain or cramping, unusual bruising or bleeding, persistent fever, rash, night sweats, significant weight loss, muscle weakness, and/or signs of respiratory infection
- Avoid receiving immunizations during therapy and for at least 3 months after therapy with TNF inhibitors

SELECTIVE COSTIMULATOR BLOCKERS

Introduction
Selective costimulator blockers block the stimulation of T cells, thus decreasing the immune response. Abatacept is a biologic disease modifying antirheumatic drug (DMARD) used in the treatment of rheumatoid arthritis, whereas belatacept is used to prevent kidney transplant rejection. These medications suppress the immune system and put patients at higher risk for infection. Therefore, patients need to be screened for latent TB infection prior to initiation.

Mechanism of Action for the Drug Class
Bind to a receptor on the surface of antigen-presenting cells (APCs), inhibiting the interaction between APCs and T cells. This prevents T cells from being activated and producing an immune response, thus preventing joint tissue destruction (abatacept) or organ transplant rejection (belatacept).

Members of the Drug Class
In this section: Abatacept
Other: Belatacept

Abatacept

Brand Name
Orencia

Generic Name
Abatacept

Rx Only

Dosage Form
Injection

Usage

Moderate to severe juvenile idiopathic arthritis (JIA) and adult rheumatoid arthritis (RA)

Pregnancy

Data in pregnant women are insufficient to inform drug-associated risk. Adverse effects were not observed in animal studies. There is a pregnancy exposure registry that monitors outcomes in pregnant women exposed to the drug.

Dosing

- IV: Infused over 30 minutes. Total dose is based on weight. Doses are given at weeks 0, 2, and 4 and then every 4 weeks thereafter:
  - < 60 kg: 500 mg
  - 60 to 100 kg: 750 mg
  - > 100 kg: 1000 mg
- SUB-Q: 125 mg within 24 hours of the IV infusion, then 125 mg SUB-Q once weekly. Can initiate SUB-Q dosing weekly if patient is unable to get first dose as IV infusion.

Adverse Reactions: Most Common

Acute exacerbation of chronic obstructive pulmonary disease (COPD), headache, nausea, infection

Adverse Reactions: Rare/Severe/Important

Infection, including reactivation of hepatitis B and tuberculosis; anaphylaxis; malignancy (lymphoma and lung cancer), anaphylaxis or hypersensitivity reaction with IV administration

Major Drug Interactions

Abatacept's Effect on Other Drugs

- TNF blockers and other concomitant immunosuppressive agents: Increase risk of infection, toxicities, and immunosuppression
- Vaccines: Efficacy of inactivated vaccines may be reduced; increase risk of developing vaccinial infections with live vaccines

Contraindications

None

Essential Monitoring Parameters

Signs and symptoms of infection, hypersensitivity reaction, hepatitis, and TB screening before starting therapy

Counseling Points

- Store in the refrigerator and protect from light
- SUB-Q administration: Allow prefilled syringe to warm to room temperature (30 to 60 minutes) prior to administration. Inject into the front of the thigh (preferred), abdomen (except for 2-inch area around the navel), or the outer area of the upper arms. Rotate injection sites (≥ 1 inch apart) and do not administer into tender, bruised, red, or hard skin.
- This drug increases susceptibility to infections; report any signs of infection to your healthcare provider
- Avoid live vaccines while on therapy or within 3 months of discontinuing therapy

Key Points

- Screen patients for latent TB infection and viral hepatitis prior to initiating therapy
- IV must be infused through a 0.2–1.2 micron low protein–binding filter
- Powder for injection contains maltose, which may falsely increase serum glucose readings on the day of infusion if using a glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ) glucose test
- Patients can develop antibodies to this product. The clinical significance of this is unknown.

INTERLEUKIN-6 RECEPTOR ANTAGONIST

Introduction

Interleukin-6 receptor antagonists block IL-6 from binding to the receptor, thus decreasing the immune response. Tocilizumab is a biologic disease modifying antirheumatic drug (DMARD) used in the treatment of rheumatoid arthritis, whereas siltuximab is used to treat multicentric Castleman disease, a lymphoproliferative disorder. These medications suppress the immune system and put patients at higher risk for infection.

Mechanism of Action for the Drug Class

Bind to IL-6 receptors and inhibit the IL-6 mediated signaling pathways that produce proinflammatory cytokines that are part of the inflammatory process. IL-6 mediated inflammatory responses are important in the pathophysiology of RA and are linked to systemic manifestations in patients with multicentric Castleman disease.

Members of the Drug Class

In this section: Tocilizumab
Other: Siltuximab

◉ Tocilizumab

Brand Name

Actemra

Generic Name

Tocilizumab

Rx Only

Dosage Form

Injection

Usage

Juvenile idiopathic arthritis (JIA), adult rheumatoid arthritis (RA)

Pregnancy

Adverse events have been observed in some animal reproductive studies. The limited data in pregnant women are not sufficient to determine the risk for major birth defects and miscarriage. There is a pregnancy exposure registry that monitors outcomes in pregnant women exposed to the drug.

Dosing

- RA:
  - Intravenous: 4 mg/kg IV every 4 weeks, may increase to 8 mg/kg every 4 weeks based on clinical response (max dose 800 mg)
  - Subcutaneous:
    - < 100 kg: 162 mg SUB-Q every other week, may increase to every week, based on clinical response
    - 100 kg: 162 mg SUB-Q every week
- Dose adjustments based on toxicities:
  - Hepatotoxicity
    - ALT/AST > 1 to 3 × ULN: For patients receiving IV therapy, reduce dose to 4 mg/kg IV or interrupt until ALT/AST have normalized. For patients receiving SUB-Q therapy, reduce injection frequency to every other week or interrupt until ALT/AST have normalized.
    - ALT/AST > 3 to 5 × ULN: Interrupt therapy until ALT/AST < 3 × ULN, then follow dosage adjustments described above for ALT/AST > 1 to 3 × ULN.
  - ANC 500–1000 cells/mm^3: Interrupt therapy and when ANC > 1000 cells/mm^3 resume 4 mg/kg IV (may increase to 8 mg/kg IV if clinically appropriate) or resume SUB-Q every other week (may increase to every week, if clinically appropriate)
  - Platelets 50,000–100,000 cells/mm^3: Interrupt therapy and when platelets > 100,000 cells/mm^3 resume 4 mg/kg IV (may increase to 8 mg/kg IV, if clinically appropriate) or resume SUB-Q every other week (may increase to every week, if clinically appropriate)
  - Discontinue therapy for ALT/AST > 5 × ULN, ANC < 500, platelets < 50,000 cells/mm^3

Adverse Reactions: Most Common

Upper respiratory tract infection, headache, hypertension, increased ALT, infusion related/injection-site reactions, increased serum cholesterol

Adverse Reactions: Rare/Severe/Important

Infection (including reactivation of hepatitis B/tuberculosis/herpes zoster, fungal, bacterial, viral, opportunistic infections), anaphylaxis, elevated liver enzymes, gastrointestinal perforation, neutropenia, thrombocytopenia, hyperlipidemia, malignancy, demyelinating CNS disease (MS)

Major Drug Interactions

Tocilizumab's Effect on Other Drugs

- TNF blockers and other concomitant immunosuppressive agents: Increase risk of infection, toxicities, and immunosuppression
- Vaccines: Efficacy of inactivated vaccines may be reduced; increase risk of developing vaccinial infections with live vaccines
- CYP3A4 substrates: Tocilizumab may decrease serum concentrations of CYP3A4 substrates

Contraindications

None

Essential Monitoring Parameters

Signs and symptoms of infection, hypersensitivity reaction, hepatitis, and TB screening before starting therapy, CBC with differential (neutrophils, platelets), LFTs, lipids

Counseling Points

- Store in the refrigerator and protect from light
- SUB-Q administration: Allow prefilled syringe to warm to room temperature (30 minutes) prior to administration. Inject into the front of the thigh (preferred), abdomen (except for 2-inch area around the navel), or the outer area of the upper arms. Rotate injection sites (≥ 1 inch apart) and do not administer into moles; scars; or tender, bruised, red, or hard skin.
- This drug increases susceptibility to infections; report any signs of infection to your healthcare provider
- Avoid live vaccines while on therapy or within 3 months of discontinuing therapy

Key Points

- **Black Box Warning:**
  - May result in serious infections leading to hospitalization or death. If serious infection develops, interrupt therapy
- Screen patients for latent TB infection prior to initiating therapy
- Screen patients for viral hepatitis prior to initiating therapy
- When transitioning from IV administration to SUB-Q administration, give the first SUB-Q dose instead of the next scheduled IV dose
- Dose adjustments and drug discontinuation may be necessary based on ALT/AST, ANC, and platelets count

JANUS KINASE INHIBITOR

Introduction

Janus kinase (JAK) enzymes play important roles in the cell signaling pathways that stimulate hematopoiesis and immune cell function. Inhibiting the actions of these enzymes decreases the immune response. Tofacitinib is a nonbiologic disease modifying antirheumatic drug (DMARD) used in the treatment of rheumatoid arthritis, whereas ruxolitinib is used to treat myelofibrosis, a bone marrow disorder that disrupts normal cell production. These medications suppress the immune system and put patients at higher risk for infection.

Mechanism of Action for the Drug Class

Inhibit JAK enzymes that are needed to activate signal transducers and activators of transcription pathways that regulate gene expression. This prevents cytokine and growth factor–mediated gene expression and intracellular activity of immune cells, thus decreasing the immune response.

Members of the Drug Class

In this section: Tofacitinib
Other: Ruxolitinib

◉ Tofacitinib

Brand Name

Xeljanz

Generic Name

Tofacitinib

Rx Only

Dosage Form

Oral tablet

Usage

Moderate to severe rheumatoid arthritis (RA)

Pregnancy Category: C

Dosing

- Immediate release: 5 mg by mouth twice daily
- Extended release: 11 mg by mouth once daily
- Dose adjustments
  - Moderate–severe renal impairment: Immediate release 5 mg by mouth once daily; has not been studied in patients with CrCl < 40 ml/min
  - Moderate hepatic impairment: Immediate release 5 mg by mouth once daily; not recommended in patients with severe hepatic impairment or hepatitis B or C
  - Anemia (hemoglobin < 8 g/dl or decrease > 2 g/dl); interrupt therapy until hemoglobin normalized
  - Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole): reduce dose to immediate release 5 mg by mouth once daily (don't use extended release)
  - Concomitant use of moderate CYP3A4 inhibitors and potent CYP2C19 inhibitors (e.g., fluconazole): Reduce dose to immediate release 5 mg by mouth once daily

Adverse Reactions: Most Common

Upper respiratory tract infection, headache, diarrhea

Adverse Reactions: Rare/Severe/Important

Infection (including reactivation of hepatitis B/tuberculosis/herpes zoster, fungal, bacterial, viral, opportunistic infections), decreased heart rate and prolonged PR interval, bone marrow suppression (lymphocytopenia, neutropenia, anemia), gastrointestinal perforation, hepatotoxicity, interstitial lung disease, increased lipids, malignancy (lymphoma, others), risk of adverse effects, higher in Asian patients (herpes zoster, opportunistic infections, decreased WBC, interstitial lung disease, increase LFTs)

Major Drug Interactions

Tofacitinib is a major CYP3A4 substrate and minor CYP2C19 substrate

Drugs Affecting Tofacitinib

- CYP3A4 inhibitors may increase serum concentrations of tofacitinib
- CYP3A4 inducers may decrease serum concentrations of tofacitinib
- Fluconazole may increase serum concentrations of tofacitinib

Tofacitinib's Effect on Other Drugs

- TNF blockers and other concomitant immunosuppressive agents: Increase risk of infection, toxicities, and immunosuppression
- Vaccines: Efficacy of inactivated vaccines may be reduced, increase risk of developing vaccinial infections with live vaccines
- CYP3A4 substrates: Tocilizumab may decrease serum concentrations of CYP3A4 substrates

Contraindications

None

Essential Monitoring Parameters

Signs and symptoms of infection, hepatitis, and TB screening before starting therapy, CBC with differential (lymphocyte, hemoglobin), LFTs, lipids, heart rate, and blood pressure

Counseling Points

- Extended release tablet: swallow tablet whole and intact, do not crush, split, or chew
- This drug increases susceptibility to infections; report any signs of infection to your healthcare provider
- Avoid live vaccines while on therapy or within 3 months of discontinuing therapy

Key Points

- **Black Box Warning:**
  - May cause serious infections, leading to hospitalization or death. If serious infection develops, interrupt therapy
- Screen patients for latent TB infection and viral hepatitis prior to initiating therapy
- Do not initiate therapy in patients with an absolute lymphocyte count < 500 cells/mm^3, ANC < 1000 cells/mm^3, or hemoglobin < 9 g/dl, and patients taking strong CYP3A4 inducers (e.g., rifampin)
- Dose adjustments recommended for patients taking strong CYP3A4 inhibitors or moderate CYP3A4 and strong CYP2C19 inhibitors

INTERLEUKIN-2 INHIBITOR

Introduction

Interleukin-2 plays a role in activating and regulating the immune response and is thought to play a role in multiple sclerosis (MS). Blocking the actions of IL-2 decreases the immune response and has therapeutic benefit in patients with MS.

Mechanism of Action for the Drug Class

Daclizumab is a humanized monoclonal antibody that binds to a subunit of the IL-2 receptor, which blocks IL-2 from binding to activated lymphocytes, thereby suppressing the immune response.

Members of the Drug Class

In this section: Daclizumab

⦿ Daclizumab

Brand Name

Zinbryta

Generic Name

Daclizumab

Rx Only

Dosage Form

Injection

Usage

Relapsing MS

Pregnancy

Adverse events have been observed in animal reproductive studies. There are no adequate data in pregnant women but use of similar agents is not recommended for the treatment of MS in pregnant women because monoclonal antibodies are known to cross the placenta.

Dosing

150 mg SUB-Q once monthly

Adverse Reactions: Most Common

Skin reaction (dermatitis, rash, eczema), autoimmune disease, upper respiratory tract infection, depression, increased ALT/AST

Adverse Reactions: Rare/Severe/Important

Hepatotoxicity (hepatic failure, autoimmune hepatitis), hypersensitivity (anaphylaxis, angioedema, urticaria), immune-mediated reactions, such as lymphadenopathy and noninfectious colitis, infection (including reactivation of hepatitis B/tuberculosis), depression, suicidal ideation/attempt

Major Drug Interactions

Daclizumab's Effect on Other Drugs

- Concomitant immunosuppressive agents: Increase risk of infection, toxicities, and immunosuppression
- Vaccines: Efficacy of inactivated vaccines may be reduced, increase risk of developing vaccinial infections with live vaccines
- Concomitant hepatotoxic drugs: Increase risk of hepatotoxicity

Contraindications

- Pre-existing hepatic disease or hepatic impairment, including ALT or AST at least two times the ULN
- History of autoimmune hepatitis or other autoimmune condition involving the liver

Essential Monitoring Parameters

Signs and symptoms of infection, hepatitis, and TB screening before starting therapy, ALT/AST, bilirubin

Counseling Points

- Store in the refrigerator and protect from light
- Allow prefilled syringe to warm to room temperature (30 minutes) prior to administration. Inject into the thigh, abdomen, or back of the upper arm.
- Call your doctor right away if you have signs of liver problems like dark urine, feeling tired, not hungry, upset stomach or stomach pain, light-colored stools, throwing up, or yellow skin or eyes
- Certain immune system problems can happen with this drug. Some of these may include skin reactions, swollen glands, and a very bad bowel problem (colitis). Call your doctor right away if you have a skin reaction like rash or skin irritation, or if you have tender, painful, or swollen lymph nodes. Call your doctor if you have signs of colitis like bloody stools, diarrhea that does not go away, fever, or stomach pain
- This drug increases susceptibility to infections; report any signs of infection to your healthcare provider
- Avoid live vaccines while on therapy or within 4 months of discontinuing therapy

Key Points

- **Black Box Warning:**
  - Associated with severe liver injury including life-threatening events, liver failure, and autoimmune hepatitis. The drug may also cause immune-mediated disorders, including skin reactions, lymphadenopathy, and noninfectious colitis.
- Due to risks of hepatotoxicity and other immune-mediated disorders, this drug is only available through a restricted program as a Risk Evaluation and Mitigation Strategy (REMS). Prescribers and pharmacies must be certified with the program and patients must be enrolled in the program and comply with ongoing monitoring requirements.
- Contraindicated in patients with liver disease
- Interrupt treatment in patients with ALT/AST > 5 × ULN *or* total bilirubin > 2 × ULN *or* ALT or AST ≥ 3 to < 5 × ULN *and* total bilirubin > 1.5 to < 2 × ULN
- Screen patients for latent TB infection prior to initiating therapy
- Screen patients for viral hepatitis prior to initiating therapy

SUPPRESSOR T CELL ACTIVATORS

Introduction

Glatiramer is used in the treatment of relapsing-remitting multiple sclerosis (MS). Like the interferons, it should be used early in the disease, because it has been shown to modify disease progression and reduce relapse rates.

Mechanism of Action for the Drug Class

Glatiramer is a synthetic polypeptide consisting of four amino acids: L-alanine, L-glutamic acid, L-lysine, and L-tyrosine. The resulting mixture mimics the protein myelin, found in the nerve sheath. As a result, glatiramer induces and activates suppressor T cells specific for a myelin antigen, thus modifying the immune process occurring against the nerves in the pathogenesis of MS.

Member of the Drug Class

In this section: Glatiramer acetate

◉ Glatiramer Acetate

Brand Name

Copaxone, Glatopa

Generic Name

Glatiramer acetate

Rx Only

Dosage Form

Injection

Usage

Multiple sclerosis

Pregnancy Category B

Dosing

Inject 20 mg SUB-Q once daily or 40 mg SUB-Q 3 times per week at least 48 hours apart

Adverse Reactions: Most Common

Transient chest pain postinjection, vasodilation, injection-site reaction, pain, weakness

Adverse Reactions: Rare/Severe/Important

Infections, anaphylaxis, injection-site necrosis

Major Drug Interactions

Other immunosuppressive agents: May increase toxic effects of both immunosuppressive agents and increase risk of serious infection

Contraindication

Hypersensitivity to mannitol

Essential Monitoring Parameters

Postinjection reaction (flushing, chest pain, dyspnea, urticaria)

Counseling Points

- Store in the refrigerator
- Prior to use, let the syringe stand at room temperature for 20 minutes to allow solution to warm to room temperature
- Syringes are single-use only; any unused portion should be discarded
- For SUB-Q administration in the arms, abdomen, hips, or thighs, rotate injection sites to prevent lipoatrophy
- May cause reaction after injection, including flushing, chest tightness, dyspnea, or palpitations. Seek medical assistance if symptoms last more than a few minutes or are intense.
- Report any signs of infection
- Avoid live vaccines while on therapy or within 3 months of discontinuing therapy

Key Points

- Because this is a biologic agent, neutralizing antibodies (IgG) can form in patients. The clinical significance of this is unknown.
- Immediate postinjection systemic reactions can occur in approximately 10% of patients, with symptoms including: chest pain, dyspnea, flushing, palpitations, and dyspnea. These symptoms can occur with any dose and are usually self-limiting and transient.

INTERFERONS

Introduction

Interferons are proteins that are released in response to the presence of pathogens, such as viruses, bacteria, parasites, or tumor cells. Synthetic interferons have been made to resemble naturally occurring interferons and to treat viral infections, such as chronic hepatitis B and chronic hepatitis C; neoplasms, such as hairy cell leukemia, lymphoma, malignant melanoma, Kaposi's sarcoma, and condylomata acuminata; and autoimmune diseases, such as multiple sclerosis. The most common adverse effects are flulike effects, such as fatigue, headache, fever, and rigors and injection-site reactions. Antibodies can form against the synthetic interferons, decreasing their effectiveness.

Mechanism of Action for the Drug Class

Synthetic interferons trigger the immune system to eradicate pathogens and neoplasms. This occurs through a multitude of different effects, including the inhibition of growth of some cells, changes in cell surface antigen expression, and induction of lymphocytic cytotoxicity. For some indications, the mechanism of action is not well established.

Members of the Drug Class

In this section: Interferon beta-1a, peginterferon beta-1a, interferon beta-1b, peginterferon alfa-2a
Others: Interferon alfa-2b, interferon alpha-n3, interferon alfacon-1, interferon gamma-1b, peginterferon alfa-2b

⦿ Interferon Beta-1a

Brand Names

Avonex, Rebif

Generic Name

Interferon Beta-1a

Rx Only

Dosage Form

Injection

Usage

Multiple sclerosis

Pregnancy Category C

Dosing

- Avonex:
  - 30 µg IM once weekly *or*
  - 7.5 µg IM in week 1, then increase dose by 7.5 mg each week until 30 µg once weekly is reached
- Rebif:
  - If target dose is 44 µg 3 times per week, start with 8.8 µg SUB-Q 3 times per week for weeks 1 and 2, then increase to 22 µg SUB-Q 3 times per week for weeks 3 and 4, then increase to 44 µg SUB-Q 3 times per week
  - If target dose is 22 µg 3 times per week, start with 4.4 µg SUB-Q 3 times per week for weeks 1 and 2, then increase to 11 µg SUB-Q 3 times per week for weeks 3 and 4, then increase to 22 µg SUB-Q 3 times per week

Adverse Reactions: Most Common

Flulike symptoms (chills, fever, myalgias, asthenia, fatigue), injection-site reactions, headache

Adverse Reactions: Rare/Severe/Important

Depression and suicide; severe liver injury, including hepatic failure; pancytopenia; autoimmune disorders (thrombocytopenia, hyper/hypothyroidism, hepatitis); seizures; congestive heart failure

Contraindications

History of hypersensitivity to natural or recombinant interferon beta or albumin

Essential Monitoring Parameters

Thyroid function tests, CBC with differential, liver function tests, signs and symptoms of psychiatric disorder

Counseling Points

- Injections:
  - The first injection must be administered under the supervision of a healthcare professional
- Rotate areas of injection with each dose to minimize the likelihood of injection-site reactions
  - Do not inject in area of the body where the skin is irritated, reddened, bruised, infected, or scarred
  - Check the injection site after 2 hours for redness, swelling, or tenderness
  - Contact your healthcare provider if you have a skin reaction that does not clear up in a few days
- Inform your healthcare provider immediately if you feel depressed or have suicidal thoughts; have chest pain or palpitations; experience pain, swelling, or redness at the injection site; or have seizures

Key Points

- Rebif is given SUB-Q and Avonex is given IM
- Pretreatment with analgesics or antipyretics on injection days may decrease flulike symptoms

Peginterferon Beta-1a

Brand Name

Plegridy

Generic Name

Peginterferon beta-1a

Rx Only

Dosage Form

Injection

Usage

Multiple sclerosis

Pregnancy Category C

Dosing

63 µg SUB-Q on day 1, 94 µg on day 15, and then 125 µg every 14 days, beginning on day 29

Adverse Reactions: Most Common

Flulike symptoms (chills, fever, myalgias, asthenia, fatigue), injection-site reactions, headache

Adverse Reactions: Rare/Severe/Important

Depression and suicide; severe liver injury, including hepatic failure; pancytopenia; autoimmune disorders (thrombocytopenia, hyper/hypothyroidism, hepatitis); seizures; congestive heart failure

Contraindications

History of hypersensitivity to natural or recombinant interferon beta or peginterferon

Essential Monitoring Parameters

Thyroid function tests, CBC with differential, liver function tests, signs/symptoms of psychiatric disorder

Counseling Points

- Administer subcutaneously in the abdomen, back of the upper arm, or thigh. Rotate injection sites.
- Do not inject in area of the body where the skin is irritated, reddened, bruised, infected, or scarred
- Inform your healthcare provider immediately if you feel depressed or have suicidal thoughts, have chest pain or palpitations, or have seizures

Key Points

- Pretreatment with analgesics or antipyretics on injection days may decrease flulike symptoms
- The pegylated form of this interferon allows for administration every 14 days compared with weekly administration of the nonpegylated form

Interferon Beta-1b

Brand Names

Betaseron, Extavia

Generic Name

Interferon Beta-1b

Rx Only

Dosage Form

Injection

Usage

Multiple sclerosis

Pregnancy Category C

Dosing

Inject 0.0625 mg SUB-Q every other day. Gradually increase dose by 0.0625 mg every 2 weeks, to a maximum dose of 0.25 mg every other day.

Adverse Reactions: Most Common

Flulike symptoms (including headache, fever, chills, malaise, diaphoresis, and myalgia), injection-site reactions, edema (caution in patients with cardiac disease or heart failure), dizziness, insomnia, rash

Adverse Reactions: Rare/Severe/Important

Leukopenia, lymphopenia, neutropenia, thrombocytopenia, anaphylaxis, hepatotoxicity, infection, injection-site necrosis, neuropsychiatric conditions (psychosis, mania, depression, suicidal behavior), hyper/hypothyroid, lupus erythematosus

Contraindications

History of hypersensitivity to natural or recombinant interferon beta, albumin, or mannitol

Essential Monitoring Parameters

Complete blood count, thyroid function test, liver function tests, signs/symptoms of psychiatric disorder

Counseling Points

- First injection should be administered under the supervision of a healthcare professional
- Sites for self-injection include outer surface of the arms, abdomen, hips, and thighs. Rotate SUB-Q injection site and do not inject into area where skin is bruised, infected, or broken.
- Use product immediately or within 3 hours of reconstitution if refrigerated and discard unused portion
- Flulike symptoms are a common side effect and usually decrease over time (average duration is about 1 week)
- Immediately report any changes in mood or thoughts of suicide to your healthcare provider

Key Points

- Flulike symptoms are reported in up to 60% of patients on treatment days. These symptoms usually improve with time (~ 1 week). Analgesics or antipyretics may be used for patients with flulike symptoms.
- Patients can develop neutralizing antibodies to this product. The clinical significance of this is unknown.

⦿ Peginterferon Alfa-2a

Brand Name

Pegasys

Generic Name

Peginterferon Alfa-2a

Rx Only

Dosage Form

Injection

Usage

Chronic hepatitis C, chronic hepatitis B

Pregnancy Category C

The combination with ribavirin is pregnancy category X

Dosing

- Chronic hepatitis C:
  - Combination therapy with ribavirin: 180 µg SUB-Q once weekly with ribavirin for 24 weeks (genotype 2 or 3) or 48 weeks (genotype 1 or 4 or coinfected with HIV)
  - Combination therapy with sofosbuvir and ribavirin: 180 µg SUB-Q once weekly with sofosbuvir and ribavirin for 12 weeks
  - Monotherapy: 180 µg SUB-Q once weekly for 48 weeks
- Chronic hepatitis B: 180 µg SUB-Q once weekly for 48 weeks
- Renal dosage adjustment: If CrCl < 30 ml/min, including hemodialysis, then 135 µg SUB-Q once weekly
- Hepatic dosage adjustment: If ALT > 5 × ULN or progressively rising above baseline, then 135 µg SUB-Q once weekly
- Dosage adjustments for laboratory abnormalities:
  - ANC < 750 cells/mm^3: 135 µg SUB-Q once weekly
  - ANC < 500 cells/mm^3: Discontinue treatment until ANC values return to > 1000 cells/mm^3. Reinstitute at 90 µg and monitor ANC.
  - Platelet < 50,000 cells/mm^3: 90 µg SUB-Q once weekly
  - Platelet < 25,000 cells/mm^3: Discontinue treatment
- Dosage adjustment for depression:
  - Moderate depression: 90 µg or 135 µg SUB-Q once weekly
  - Severe depression: Discontinue permanently

Adverse Reactions: Most Common

Flulike side effects (fatigue, headache, fever, and rigors), myalgias, headaches, GI intolerance (nausea, vomiting, diarrhea), alopecia, psychiatric side effects (depression, irritability, and insomnia), injection-site reactions, neutropenia, anemia

Adverse Reactions: Rare/Severe/Important

Neuropsychiatric (depression, suicidal ideation, suicide, homicidal ideation, relapse of drug addiction, drug overdose), pancytopenia, cardiovascular (supraventricular arrhythmias, chest pain, and myocardial infarction), autoimmune disorders, infections, pancreatitis, gastrointestinal hemorrhage, colitis, hepatic decompensation, ischemic and hemorrhagic cerebrovascular events, ophthalmic (decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, papilledema and serous retinal detachment), hyper/hypothyroidism, hyper/hypoglycemia

Major Drug Interactions

Peginterferon afa-2a can increase concentrations of theophylline and methadone

Contraindications

Autoimmune hepatitis; hepatic decompensation in cirrhotic patients before treatment; neonates; infants; known hypersensitivity reactions, such as urticaria, angioedema, bronchoconstriction; and anaphylaxis to alpha interferons

Essential Monitoring Parameters

CBC (including hemoglobin, WBC, and platelets), serum chemistries (including liver function tests and uric acid), renal function; pregnancy test, TSH and T4, mental health

Counseling Points

- If you are taking peginterferon alfa-2a with ribavirin, you or your sexual partner must not be pregnant throughout treatment and until 6 months after discontinuation of treatment
- Peginterferon alfa-2a is given by injection once a week under the skin (SUB-Q injection). Administer in the abdomen or thigh and rotate injection sites.
- Take your prescribed dose of peginterferon alfa-2a on the same day each week and at approximately the same time
- Do not switch to another brand of peginterferon without talking to your healthcare provider
- Avoid drinking alcohol to reduce the chance of further liver injury
- Call your healthcare provider right away if you experience any of the following problems while taking peginterferon alfa-2a:
  - New or worsening mental health problems, such as thoughts of hurting yourself or others
  - Feeling cold or hot all of the time
  - Unusual bleeding or bruising
  - Nausea, vomiting, diarrhea, or abdominal pain
  - Changes in vision or changes to your eyes
  - Trouble breathing or chest pain
  - Any new weakness, loss of coordination, or numbness
  - Symptoms of infection, including fever, chills, burning or pain on urination, urinating often, tiredness, or coughing up yellow or pink mucus (phlegm)

Key Points

- **Black Box Warning:**
  - May cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, or infectious disorders
- Peginterferon alfa-2a monotherapy is not recommended for treatment of chronic hepatitis C unless a significant contraindication or intolerance to ribavirin is present
- Because peginterferon alfa-2a is often given with ribavirin for chronic hepatitis C, refer to ribavirin use before administering peginterferon alfa-2a
- Do not confuse peginterferon alfa-2a with peginterferon alfa-2b (PEG-INTRON), which differs in dosing
- Dose adjustments are recommended based on renal and liver function, ANC and platelet counts, and depressive symptoms

IMMUNE GLOBULINS

Introduction

Immune globulin G (IgG) is collected during blood donation and pooled for administration as a separate product for patients with a variety of medical needs. These products, widely referred to as IVIG, are used for a wide variety of indications in which acquisition of antibodies is needed. These include instances of antibody deficiency, as well as in the treatment of autoimmune and inflammatory conditions. Because these are blood product derivatives, patients can develop infusion reactions while they are being administered.

Mechanism of Action for the Drug Class

Immune globulins replace native antibodies in patients with antibody deficiencies, provide passive immunity by increasing antibody titers, and suppress inflammatory and/or autoimmune processes

Members of the Drug Class

In this section: Immune globulin
Others: Antithymocyte globulin, botulism immune globulin, cytomegalovirus immune globulin, hepatitis B immune globulin, rabies immune globulin, Rh_0(D) immune globulin, tetanus immune globulin, vaccinia immune globulin, varicella-zoster immune globulin

◉ Immune Globulin

Brand Names

Bivigam, Carimune, Cuvitru, Flebogamma, GamaSTAN, Gammagard, Gammaked, Gammaplex, Gamunex, Hizentra, Octagam, Privigen,

Generic Name

Immune globulin (IG)

Rx Only

Dosage Form

Injection

Usage

Replacement for primary or secondary immunodeficiencies, treatment of acute or chronic immune (idiopathic) thrombocytopenia purpura (ITP), prevention of bacterial infections in transplant patients with severe hypogammaglobulinemia, prevention of renal transplant rejection, chronic inflammatory demyelinating polyneuropathy (CIDP), Guillain–Barré syndrome, remitting relapsing MS, multifocal motor neuropathy, myasthenia gravis, sepsis, Kawasaki disease

Pregnancy Category C

Dosing

- ITP:
  - Carimune: 400 mg/kg per day IV for 2 to 5 days as initial dose, then 400 mg/kg as needed to maintain platelet count ≥ 30,000/mm^3 and/or control significant bleeding. Can increase dose if inadequate response to 800–1000 mg/kg IV as single dose.
  - Gammagard: 1000 mg/kg IV, can be repeated for up to three additional doses to be given on alternate days
  - Flebogamma, Gammaked, Gamunex, Privigen: 1000 mg/kg per day IV for 2 consecutive days
- Primary immunodeficiency:
  - IV: Dosing depends on product being used; 200–800 mg/kg IV infusion every 3 to 4 weeks
  - SUB-Q: Weekly SUB-Q infusion beginning 1 week after IV dose; initial weekly dose (grams) = [1.37 × IGIV dose (grams)] divided by [IV dose interval (weeks)]; adjust doses based on clinical response and trough serum IgG levels
  - IM: GamaSTAN 0.25–1.2 ml/kg IM every 3 to 4 weeks, double dose given at onset of therapy
- Renal dosage adjustment:
  - Administer IV and SUB-Q infusion at minimum infusion rate possible in patients with renal impairment. Discontinue if renal function deteriorates during treatment.

Pharmacokinetic Monitoring

For SUB-Q infusion, monitor IgG trough levels every 2 to 3 months before and after conversion from IV when giving for chronic or long-term use

Adverse Reactions: Most Common

Infusion reaction with hypotension, tachycardia, fever, chills, nausea, vomiting; injection-site reaction; myalgia; headache

Adverse Reactions: Rare/Severe/Important

Anaphylaxis/hypersensitivity reaction, hyperproteinemia, transfusion-related acute lung injury, acute renal failure, aseptic meningitis syndrome, hemolytic anemia, thrombotic events

Major Drug Interactions

Immune Globulin's Effect on Other Drugs

Live vaccines: Immune globulins may diminish therapeutic effect of live vaccines

Contraindications

Severe thrombocytopenia or any coagulation disorder that would contraindicate IM injections, IgA deficiency with antibodies against IgA

Essential Monitoring Parameters

Renal function, urine output, hemoglobin and hematocrit, platelet count (in ITP), volume status, anaphylaxis, signs and symptoms of thrombosis, neurologic symptoms for aseptic meningitis

Counseling Points

- Immune globulin is made from human plasma and may have viruses that can cause disease. This drug is screened, tested, and treated to decrease the chance that it carries an infection.
- Report any signs of infection
- Monitoring will be required during IV infusion or SUB-Q administration. Report any chills, chest pain or tightness, rapid heartbeat, back pain, or difficulty breathing to your healthcare provider.

Key Points

- **Black Box Warnings:**
  - Acute renal dysfunction may occur rarely with IV administration only and is usually within 7 days of use. Thrombosis can occur with immune globulin products, even in the absence of risk factors for thrombosis.
- Live vaccines should be withheld for up to 6 months following immune globulin administration. Live vaccine given immediately prior to immune globulin administration may require repeat vaccination.
- Octagam contains maltose and can falsely elevate blood glucose levels if measured using the glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ) methods
- Storage varies based on product. Some formulations require refrigeration.
- Dosing varies based on product used
- IV administration: Initial rate of administration and titration is specific to each IVIG product
- SUB-Q administration: Appropriate injection sites include the abdomen, thigh, upper arm, lower back, and/or lateral hip. Dose may be infused into multiple sites (spaced ≥ 2 inches apart) simultaneously. Rotate sites weekly.
- IM administration: Appropriate injection sites include anterolateral aspects of the upper thigh or deltoid muscle of the upper arm. Avoid gluteal region due to risk of injury to sciatic nerve. Divide doses > 10 ml and inject in multiple sites.

BOTULINUM TOXIN

Introduction

Botulinum toxin is a neurotoxic protein derived from *Clostridium botulinum*, the bacterium responsible for botulism. It is one of the most potent toxins known and inhibits neurotransmission between peripheral nerve endings and muscle fibers, thus paralyzing skeletal muscle. When ingested systemically, botulism can be rapidly fatal. Botulinum toxin types A and B are administered locally and are used for numerous medical indications, such as dystonia, spasticity, migraine, and bladder dysfunction, as well as cosmetically.

Mechanism of Action

Botulinum toxin prevents muscle contraction by inhibiting the release of acetylcholine from peripheral nerve cells into neuromuscular junctions.

Members of the Drug Class

In this section: OnabotulinumtoxinA
Others: AbobotulinumtoxinA, IncobotulinumtoxinA, RimabotulinumtoxinB

◉ OnabotulinumtoxinA

Brand Names

Botox, Botox Cosmetic

Generic Name

OnabotulinumtoxinA

Rx Only

Dosage Form

Injection

Usage

Medical: Cervical dystonia, chronic migraine, upper and lower limb spasticity, overactive bladder, axillary hyperhidrosis, dystonia
Cosmetic: Treatment of lines and wrinkles

Pregnancy Category C

Dosing

- Cervical dystonia: The mean dose is 236 units IM divided among the affected muscles
- Chronic migraine: Recommended total dose is 155 units IM once every 12 weeks, divided and administered bilaterally into 31 sites across the head
- Spasticity: Dose is administered IM and individualized based on patient size, degree of spasticity, location of muscle involvement, and response to prior treatment. The lowest recommended starting dose should be used and ≤ 50 units per site should be administered.
- Overactive bladder: 20 injections of 0.5 ml (10 units/ml) for a total dose of 100 units/10 ml injected into the bladder. Repeat at intervals ≥ 12 weeks

Adverse Reactions: Most Common

- Cervical dystonia: Dizziness, numbness, soreness, back pain, stiffness, weakness
- Chronic migraines: Headache, neck pain, myasthenia, stiffness, muscle spasm, pain at injection site
- Spasticity: Limb pain, back pain, pain at injection site
- Overactive bladder: Dysuria, bacteriuria, hematuria, constipation, myasthenia

Adverse Reactions: Rare/Severe/Important

- Anaphylaxis and hypersensitivity reactions have occurred, including soft tissue edema, urticaria, and dyspnea
- Arrhythmia and myocardial infarction have occurred in patients with preexisting cardiovascular disease
- Bronchitis and upper respiratory infection have been reported in patients being treated for upper or lower limb spasticity
- Dysphagia is common when onabotulinumtoxinA is used for cervical dystonia and may persist anywhere from 2 weeks to 5 months after administration
- Therapy for overactive bladder increases the incidence of urinary tract infections

Major Drug Interactions

Drugs Affecting OnabotulinumtoxinA

- Aminoglycosides: May enhance the neuromuscular blocking effects of OnabotulinumtoxinA
- Anticholinergic agents: May enhance the anticholinergic effects of OnabotulinumtoxinA
- Neuromuscular blocking agents: May enhance the neuromuscular blocking effect of OnabotulinumtoxinA

Contraindications

OnabotulinumtoxinA is contraindicated in patients with an infection at the proposed injection site

Counseling Points

- Patients may experience injection-site reactions, neck pain, headache, dry eye, and dry mouth
- Patients should immediately report any signs of infection, difficulty breathing, dysphagia, difficulty speaking, vision changes, severe muscle weakness, or urinary retention

Key Points

- **Black Box Warnings:**
  - Distant spread of botulinum toxin beyond the site of injection has been reported; dysphagia and breathing difficulties have occurred and may be life threatening
- The lowest recommended dose should be used when initiating treatment. In adults, the maximum cumulative dose should be < 400 units/ 3 months.
- Botulinum products (abobotulinumtoxinA, onabotulinumtoxinA, rimabotulinumtoxinB) are not interchangeable; potency units are specific to each preparation
- Caution is recommended if there is inflammation or excessive weakness or atrophy at the injection site. Use is contraindicated if infection is present.

REVIEW QUESTIONS

1. Which of the following is a Black Box Warning with onabotulinumtoxinA?
   a. Dysphagia
   b. Upper respiratory infection
   c. Myasthenia
   d. Spasticity

2. The immune globulins may diminish the effect of which of the following drugs?
   a. Aminoglycosides
   b. Live vaccines
   c. The interferons
   d. Corticosteroids

3. A common, self-limiting, and transient adverse effect that occurs in up to 10% of patients receiving Copaxone is:
   a. Formation of neutralizing antibodies
   b. Acute renal insufficiency
   c. Thrombosis
   d. Postinjection systemic reactions

4. Which pregnancy category is mycophenolic acid?
   a. B
   b. C
   c. D
   d. X

5. Which of the following patients are NOT indicated to receive the hepatitis B vaccine?
   a. Healthcare workers
   b. Pregnant patients
   c. HIV patients
   d. Injection drug users

6. What is the typical age at which the human papillomavirus vaccine is offered to females and males, assuming there is no history of sexual abuse or sexual assault?
   a. 9 years old
   b. 11 or 12 years old
   c. 16 years old
   d. 25 years old

7. All of the following are possible adverse effects of tacrolimus, except:
   a. Nephrotoxicity
   b. QT prolongation
   c. Tremor
   d. Hypotension

8. Which of the following is a live, attenuated vaccine?
   a. Human papillomavirus vaccine
   b. Measles, mumps, and rubella vaccine
   c. Pneumococcal conjugate vaccine (13-valent)
   d. Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap)

9. A common adverse reaction of the immune globulins is
   a. Hepatitis
   b. Aseptic meningitis
   c. Infusion reaction
   d. Hemolytic anemia

10. What is the therapeutic range for a cyclosporine trough level?
    a. 5–20 ng/ml
    b. 25–200 ng/ml
    c. 10–20 ng/ml
    d. 400–800 ng/ml

11. A typical dose for glatiramer for multiple sclerosis is

- **a.** 100 mg SUB-Q daily
- **b.** 20 mg SUB-Q daily
- **c.** 50 mg IV monthly
- **d.** 150 mg SUB-Q daily

12. Which of the following drugs could enhance the neuromuscular blocking activity of onobotulinumtoxinA?

- **a.** Diphenhydramine
- **b.** Methadone
- **c.** Erythromycin
- **d.** Gentamicin

13. Which of the following drugs decreases the absorption of mycophenolic acid?

- **a.** Antacids
- **b.** Probenecid
- **c.** Oral contraceptives
- **d.** Tacrolimus

14. Which of the following vaccines is contraindicated in infants with moderate to severe acute gastroenteritis?

- **a.** Influenza vaccine
- **b.** Pneumococcal conjugate vaccine (13-valent)
- **c.** Rotavirus vaccine
- **d.** Hepatitis B vaccine

15. Which of the following drugs is necessary to be dose adjusted in renal and hepatic insufficiency?

- **a.** Interferon Beta-1a
- **b.** Tacrolimus
- **c.** Infliximab
- **d.** Glatiramer

16. Which of the following disease modifying antirheumatic drugs (DMARDs) is available as an oral tablet?

- **a.** Daclizumab
- **b.** Tofacitinib
- **c.** Abatacept
- **d.** Etanercept

17. Which of the following is a Black Box Warning for daclizumab?

- **a.** Severe liver injury
- **b.** Severe renal injury
- **c.** Dysphagia and breathing difficulty
- **d.** Opportunistic infections

18. Which of the following medications has a Black Box Warning for causing neuropsychiatric symptoms, including suicidal ideation?

- **a.** Poliovirus vaccine
- **b.** Cyclosporine
- **c.** Adalimumab
- **d.** Peginterferon Alfa-2a

19. Screening for hepatitis B and tuberculosis is necessary prior to taking all of the following medications, except:

- **a.** Tacrolimus
- **b.** Certolizumab pegol
- **c.** Tocilizumab
- **d.** Daclizumab

20. For which of the following medications is a biosimilar product available?

- **a.** Mycophenolate mofetil
- **b.** Interferon Beta-1b
- **c.** Infliximab
- **d.** Golimumab

21. Which of the following vaccines provides protection from invasive disease caused by *Neisseria meningitidis* serogroups A, C, Y, and W-135?

- **a.** Bexsero
- **b.** Menactra
- **c.** Rotarix
- **d.** Prevnar

22. The *Haemophilus influenzae* type B vaccine is a live attenuated vaccine.

- **a.** True
- **b.** False

23. The TNF blocking medications have a Black Box Warning for causing which of the following?

- **a.** Peripheral neuropathy
- **b.** Colitis
- **c.** Heart failure
- **d.** Malignancy

24. Which of the following medications is only available through a Risk Evaluation and Mitigation Strategy (REMS) program?

- **a.** Glatiramer
- **b.** Immune globulin
- **c.** Daclizumab
- **d.** OnabotulinumtoxinA

25. Which of the following medications is used for the treatment of hepatitis C?

- **a.** Peginterferon Alfa-2a
- **b.** Interferon Beta-1a
- **c.** Flebogamma
- **d.** Hiberix

26. Which of the following is true regarding the poliovirus vaccine?

- **a.** It is given by the oral route
- **b.** It is an inactivated vaccine
- **c.** It is contraindicated in children less than 2 years of age
- **d.** It should only be given to children traveling to hyperendemic areas

27. TNF blocking medications are used for the treatment of all of the following, except:

- **a.** Rheumatoid arthritis
- **b.** Crohn's disease
- **c.** Ulcerative colitis
- **d.** Multiple sclerosis

28. Tocilizumab has recommendations to interrupt therapy if which parameter is out of range?

- **a.** Hemoglobin
- **b.** CrCl
- **c.** Blood pressure
- **d.** ANC

29. Tofacitinib is likely to interact with which of the following medications?

- **a.** Pantoprazole
- **b.** Fluconazole
- **c.** Sertraline
- **d.** Rosuvastatin

30. A patient who just received the varicella virus vaccine should not take which of the following?

- **a.** Acetaminophen
- **b.** Amlodipine
- **c.** Acyclovir
- **d.** Antacids

Answer Key

Chapter 1

1.	A	**11.**	A	**21.**	D
2	B	**12.**	D	**22.**	A
3.	A	**13.**	A	**23.**	A
4.	D	**14.**	C	**24.**	B
5.	C	**15.**	C	**25.**	C
6.	B	**16.**	C	**26.**	A
7.	A	**17.**	B	**27.**	C
8.	C	**18.**	D	**28.**	D
9.	A	**19.**	A	**29.**	D
10.	B	**20.**	A	**30.**	C

Chapter 2

1.	B	**11.**	B	**21.**	C
2.	D	**12.**	C	**22.**	C
3.	D	**13.**	C	**23.**	C
4.	B	**14.**	D	**24.**	A
5.	C	**15.**	B	**25.**	B
6.	C	**16.**	D	**26.**	A
7.	A	**17.**	A	**27.**	D
8.	A	**18.**	C	**28.**	B
9.	A	**19.**	D	**29.**	D
10.	D	**20.**	C	**30.**	C

Chapter 3

1.	B	**11.**	B	**21.**	B
2.	C	**12.**	C	**22.**	A
3.	D	**13.**	A	**23.**	C
4.	B	**14.**	C	**24.**	B
5.	A	**15.**	B	**25.**	D
6.	D	**16.**	D	**26.**	C
7.	C	**17.**	A	**27.**	D
8.	A	**18.**	B	**28.**	B
9.	D	**19.**	C	**29.**	D
10.	B	**20.**	D	**30.**	B

Chapter 4

1.	A	**11.**	B	**21.**	D
2.	D	**12.**	C	**22.**	B
3.	A	**13.**	B	**23.**	B
4.	C	**14.**	C	**24.**	A
5.	C	**15.**	A	**25.**	B
6.	D	**16.**	B	**26.**	B
7.	C	**17.**	C	**27.**	B
8.	D	**18.**	B	**28.**	A
9.	A	**19.**	A	**29.**	C
10.	B	**20.**	D	**30.**	A

Chapter 5

1.	C	**11.**	A	**21.**	A
2.	A	**12.**	A	**22.**	C
3.	D	**13.**	D	**23.**	B
4.	D	**14.**	B	**24.**	C
5.	D	**15.**	D	**25.**	D
6.	D	**16.**	D	**26.**	A
7.	D	**17.**	B	**27.**	D
8.	A	**18.**	A	**28.**	D
9.	A	**19.**	D	**29.**	B
10.	A	**20.**	C	**30.**	D

Chapter 6

1.	B	**11.**	D	**21.**	B
2.	B	**12.**	D	**22.**	C
3.	A	**13.**	C	**23.**	A
4.	B	**14.**	D	**24.**	A
5.	D	**15.**	B	**25.**	A
6.	B	**16.**	A	**26.**	B
7.	C	**17.**	A	**27.**	D
8.	A	**18.**	A	**28.**	B
9.	D	**19.**	B	**29.**	C
10.	A	**20.**	C	**30.**	C

Chapter 7

1.	B	**11.**	A	**21.**	B
2.	B	**12.**	C	**22.**	C
3.	B	**13.**	B	**23.**	D
4.	D	**14.**	D	**24.**	A
5.	A	**15.**	C	**25.**	C
6.	C	**16.**	D	**26.**	A
7.	B	**17.**	D	**27.**	B
8.	C	**18.**	C	**28.**	C
9.	C	**19.**	A	**29.**	C
10.	C	**20.**	A	**30.**	B

Chapter 8

1.	C	**11.**	A	**21.**	A
2.	D	**12.**	D	**22.**	B
3.	C	**13.**	A	**23.**	D
4.	B	**14.**	A	**24.**	C
5.	A	**15.**	D	**25.**	C
6.	D	**16.**	B	**26.**	D
7.	B	**17.**	A	**27.**	C
8.	D	**18.**	B	**28.**	B
9.	B	**19.**	B	**29.**	B
10.	B	**20.**	B	**30.**	A

Chapter 9

1.	A	**11.**	C	**21.**	C
2.	B	**12.**	A	**22.**	C
3.	B	**13.**	B	**23.**	B
4.	A	**14.**	A	**24.**	D
5.	C	**15.**	B	**25.**	B
6.	B	**16.**	A	**26.**	A
7.	C	**17.**	A	**27.**	B
8.	D	**18.**	B	**28.**	D
9.	A	**19.**	B	**29.**	D
10.	A	**20.**	C	**30.**	A

Chapter 10

1.	A	**11.**	C	**21.**	B
2.	B	**12.**	A	**22.**	A
3.	C	**13.**	A, B	**23.**	C
4.	A	**14.**	B	**24.**	A
5.	B	**15.**	B	**25.**	A
6.	C	**16.**	A	**26.**	D
7.	A	**17.**	D	**27.**	C
8.	A	**18.**	A	**28.**	A
9.	A	**19.**	A	**29.**	A
10.	A, B	**20.**	B	**30.**	A

Chapter 11

1.	C	**11.**	C	**21.**	B
2.	B	**12.**	D	**22.**	A
3.	D	**13.**	A	**23.**	B
4.	A	**14.**	D	**24.**	D
5.	B	**15.**	C	**25.**	D
6.	A	**16.**	A	**26.**	A
7.	C	**17.**	B	**27.**	C
8.	A	**18.**	A	**28.**	B
9.	C	**19.**	B	**29.**	C
10.	A	**20.**	C	**30.**	A

Chapter 12

1.	D	**11.**	C	**21.**	B
2.	C	**12.**	C	**22.**	C
3.	B	**13.**	D	**23.**	B
4.	B	**14.**	B	**24.**	C
5.	C	**15.**	B	**25.**	D
6.	B	**16.**	B	**26.**	B
7.	D	**17.**	C	**27.**	C
8.	C	**18.**	B	**28.**	C
9.	C	**19.**	B	**29.**	A
10.	A	**20.**	C	**30.**	B

Chapter 13

1.	C	**11.**	B	**21.**	C
2.	B	**12.**	D	**22.**	A
3.	A	**13.**	C	**23.**	B
4.	A	**14.**	B	**24.**	D
5.	D	**15.**	B	**25.**	B
6.	C	**16.**	C	**26.**	D
7.	D	**17.**	B	**27.**	D
8.	D	**18.**	C	**28.**	D
9.	C	**19.**	C	**29.**	D
10.	D	**20.**	C	**30.**	C

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2.	E	**12.**	D	**22.**	C
3.	B	**13.**	B	**23.**	A
4.	C	**14.**	D	**24.**	C
5.	C	**15.**	A	**25.**	B
6.	D	**16.**	B	**26.**	D
7.	C	**17.**	D	**27.**	D
8.	B	**18.**	A	**28.**	C
9.	A	**19.**	D	**29.**	B
10.	E	**20.**	A	**30.**	A

Chapter 15

1.	D	**11.**	D	**21.**	A
2.	B	**12.**	A	**22.**	A
3.	A	**13.**	C	**23.**	A
4.	A	**14.**	D	**24.**	C
5.	A	**15.**	B	**25.**	A
6.	D	**16.**	A	**26.**	C
7.	A	**17.**	C	**27.**	C
8.	D	**18.**	B	**28.**	A
9.	D	**19.**	B	**29.**	D
10.	D	**20.**	A	**30.**	D

Chapter 16

1.	A	**11.**	B	**21.**	B
2.	B	**12.**	D	**22.**	B
3.	D	**13.**	A	**23.**	D
4.	C	**14.**	C	**24.**	C
5.	B	**15.**	B	**25.**	A
6.	B	**16.**	B	**26.**	B
7.	D	**17.**	A	**27.**	D
8.	B	**18.**	D	**28.**	D
9.	C	**19.**	A	**29.**	B
10.	B	**20.**	C	**30.**	C

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