CHAPTER 1

Analgesics

Rachel Clark-Vetri, PharmD, BCOP

Drug Class: Miscellaneous Analgesics

Introduction

Three commonly used analgesics fall into categories of their own and are discussed here. Acetaminophen, one of the most commonly used analgesics, is generally well-tolerated but noted for its hepatotoxicity when given in doses exceeding daily recommendations. Butalbital combinations are most frequently used to treat headaches. Tramadol, which is used for moderate pain, also has proven efficacy for neuropathic pain.

Members of the Drug Class

In this section: Acetaminophen, butalbital with caffeine and acetaminophen, tramadol

Acetaminophen

Mechanism of Action

Inhibits brain prostaglandin synthesis, leading to analgesic and antipyretic activity

Brand Names

Tylenol, Various

Generic Name

Acetaminophen

Dosage Forms

Tablets oral and chewable, capsules, gelcaps, elixir, solutions, suppositories

Usage

- Mild pain such as headaches and arthritis pain*, fever*, combined with other analgesics for moderate–severe pain*

Dosing

- Usual dose: 500–650 mg PO every 4–6 hours as needed; maximum adult dose: 4 g/day
- Children: 10–15 mg/kg per dose every 4–6 hours as needed
- Hepatic dosage adjustment: Limit to 2 g/day in chronic alcoholics

Adverse Reactions: Most Common

- Nontoxic at therapeutic doses

Adverse Reactions: Rare/Severe/Important

- Hepatotoxicity with excessive dosing

Major Drug Interactions

Drugs Affecting Acetaminophen

- Ethanol use: >3 drinks/day may increase risk of hepatotoxicity
- Isoniazid: May increase the risk of hepatotoxicity

Acetaminophen's Effect on Other Drugs

- Warfarin: Increased anticoagulant effect

Counseling Points

- Report unresolved pain or fevers to your doctor
- Adults: Do not use >4 g/day

Key Points

- Use with caution in patients with glucose-6-phosphate dehydrogenase deficiency
- Many OTC cold and pain products contain acetaminophen, and patients should be warned to avoid inadvertently overdosing on acetaminophen by taking them in excessive combinations
- Acetaminophen is the preferred analgesic during pregnancy and breastfeeding

Butalbital with Caffeine and Acetaminophen

Mechanism of Action

Butalbital is a barbiturate that depresses the sensory cortex and depresses motor activity producing sedation and drowsiness. Caffeine increase cAMP and acts as a vasoconstrictor and a CNS stimulant. The combination is commonly used to treat headaches.

Brand Names

Fioricet, Zebutal, Dolgic Plus

Generic Names
Butalbital, acetaminophen, caffeine

Dosage Forms
Tablets, capsules, oral liquid; tablets, capsules, and 15 ml of the liquid each contain 50 mg of butalbital, 40 mg of caffeine, and 325–750 mg of acetaminophen

Usage
- Relief of tension or muscle contraction headaches*

Dosing
- Initial: 1–2 tablets or capsules (or 15–30 ml solution) every 4 hours; not to exceed 6 tablets or capsules (or 180 ml solution) daily
- Renal dosage adjustment:
  - Dosing should be reduced
- Hepatic dosage adjustment:
  - Dosing should be reduced

Adverse Reactions: Most Common
- Drowsiness, depression, nervousness, insomnia, nightmares, nausea

Adverse Reactions: Rare/Severe/Important
- Hallucinations, hypotension, respiratory and CNS depression, tachycardia, 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
- Ethanol use: >3 drinks/day may increase risk of hepatotoxicity
- Isoniazid: May increase the risk hepatotoxicity

Butalbital with Caffeine and Acetaminophen's Effect on Other Drugs
- Calcium channel blockers, contraceptives, corticosteroids, cyclosporine, disopyramide, doxycycline, tricyclic antidepressants, voriconazole, warfarin: Increase the metabolism of these agents

Counseling Points
- Report unresolved headache to your doctor
- Do not use more than the recommended daily dose

Key Point
- Many OTC cold and pain products contain acetaminophen and can increase the risk of hepatotoxicity when taken with butalbital, acetaminophen, and caffeine combinations

Tramadol

Mechanism of Action
Binds to μ-opioid receptors altering the perception and response to pain and inhibits reuptake of serotonin and norepinephrine.

Brand Names
Ultram, Ultram ER, Ultracet

Generic Name
Tramadol

Dosage Forms
Immediate-release and extended-release tablets; Ultracet is a combination with acetaminophen

Usage
- Moderate* to severe pain, neuropathic pain

Dosing
- Initial dose: 50 mg PO every 4–6 hours as needed
- Maintenance dose: 50–100 mg every 4–6 hours as needed
- Maximum dose: 400 mg/day; 300 mg/day extended-release products
- Hepatic dosage adjustment:
  - 50 mg every 12 hours
- Renal dosage adjustment:
  - 50–100 mg every 12 hours (200 mg/day maximum)

Adverse Reactions: Most Common
- Sedation, dizziness, constipation, nausea and vomiting, somnolence, euphoria/dysphoria

Adverse Reactions: Rare/Severe/Important
- Hypotension, seizures at ≥500 mg/day, abstinence syndrome with abrupt discontinuation

Major Drug Interactions
Drugs Affecting Tramadol
- Carbamazepine decreases tramadol levels
- 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

Counseling Points
- May cause drowsiness
- Abrupt discontinuation may result in withdrawal symptoms

Key Points
- Serotonin syndrome or seizures can occur when combined with antidepressants
- Use with caution in patients with a seizure history
- Tramadol has the potential for abuse

Drug Class: Narcotic Analgesics

Introduction

Narcotic analgesics are common medications used for moderate and severe pain. Given by a variety of different routes of administration and effective for both nociceptive and neuropathic pain symptoms, narcotics are controlled substances with a risk of abuse and diversion.

Members of the Drug Class

In this section: Fentanyl, hydromorphone, methadone, morphine, oxycodone

Others: Alfentanil, buprenorphine, butorphanol, levorphanol, meperidine, nalbuphine, opium tincture, oxymorphone, pentazocine, propoxyphene, remifentanil, sufentanil

Fentanyl

Mechanism of Action

Acts as an μ-opioid receptor agonist, altering the perception and response to pain centrally and peripherally

Brand Names

Actiq, Duragesic, Fentora, Sublimaze, Onsolis

Generic Name

Fentanyl

Dosage Forms

Transdermal patch, buccal tablets, film, lozenges, and injection

Usage

- Severe pain*

Dosing

- Initial dose: 12.5–25 μg/hour transdermal patch every 72 hours; 200 μg buccally every 3 hours as needed; 50–100 μg IV single dose; 1 μg/kg per hour IV infusion
- Maintenance dose: Titrate to response
- Maximum dose: Usually 4 patches for the transdermal system (limited by skin surface area); no maximum dose based on efficacy

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

Counseling Points

- Wear 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
- 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 doctor if pain is unrelieved
- A new prescription is required for any refill

Key Points

- Avoid use within 14 days of using an MAO inhibitor
- Do not wear transdermal patches during MRI
- Fever can increase absorption of fentanyl
- Controlled substance schedule II
- Short-acting narcotics should be prescribed concurrently for breakthrough pain
- When converting patients to fentanyl patch from another narcotic, use a recommended equivalent dose
- Do not use buccal and transdermal fentanyl in narcotic naïve patients for acute and postoperative pain
- Use preservative-free solution for epidural and intrathecal use

Hydromorphone

Brand Name

Dilaudid

Generic Name

Hydromorphone

Dosage Forms

Liquid oral, immediate-release tablets, injection, suppository

Usage

- Moderate to severe pain*, antitussive

Dosing
- Children:
  - Oral: 0.03–0.08 mg/kg per dose every 4 hours as needed
  - IV, IM, SUB-Q: 0.015 mg/kg per dose every 3–4 hours as needed
  - Antitussive dose: 0.5 mg every 3–6 hours
- Initial adult dose:
  - Oral: 2–4 mg every 4 hours as needed
  - SUB-Q, IV, IM: 0.2–0.6 mg every 2–4 hours as needed
  - Epidural: 1–1.5 mg bolus; 0.04–0.4 mg/hour
- Maintenance adult dose:
  - Oral: 2–8 mg PO every 3–4 hours as needed
  - IV, SUB-Q continuous range: 0.1–0.5 mg/hour
  - Rectal: Every 4 hours
- Maximum dose:
  - Oral, IV, SUB-Q: No maximum dose; titrate to response
- Renal dosage adjustment:
  - None needed

Adverse Reactions: Most Common
- Constipation, nausea, vomiting, sedation, dizziness, xerostomia, pruritis (histamine release)

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 effect
- MAO inhibitors, SSRIs: Serotonin syndrome

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 hydromorphone may result in an abstinence syndrome
- Notify your doctor if pain is unrelieved
- A new prescription is required for any refill

Key Points
- Controlled substance schedule II
- Very soluble in injectable form; useful for continuous pump and epidural or intrathecal administration

Methadone

Brand Names
Methadose, Dolophine

Generic Name
Methadone

Dosage Forms
Tablets, dispersible tablets, injection, oral solution

Usage
- Severe pain*, detoxification for opiate addiction* (as part of a program)

Dosing
- Severe pain:
  - Initial dose: 5 mg PO every 6–8 hours; 2.5–10 mg IV every 8–12 hours
  - Maintenance dose: 15–60 mg daily in divided doses
  - Maximum dose: No maximum dose; titrate to response; no ceiling effect
- Addiction:
  - Initial dose: 20–30 mg single daily dose
  - Maintenance: 40–120 mg single daily dose
- Renal dosage adjustment:
  - CrCl <10 ml/minute: Reduce dose 50–75%
- Hepatic dosage adjustment:
  - 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
- NNRTIs and 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

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 doctor if pain is unrelieved
- A new prescription is required for any refill

Key Points
- May prolong QT interval and increase risk for torsade de pointes. Patients should be evaluated for risk. ECG monitoring may be necessary within 1 month of initiation and annually.
- Controlled substance schedule II
- 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

Morphine

Brand Names
Astramorph, Avinza, Kadian, MS Contin, Oramorph, Roxanol, Various

Generic Name
Morphine

Dosage Forms
Immediate- and sustained-release tablets, injection, oral solution, suppositories

Usage
- Moderate to severe pain*

Dosing
- Children:
  - Oral: 0.2–0.5 mg/kg per dose every 4 hours as needed
  - IV, IM, SUB-Q: 0.1–0.2 mg/kg per dose every 2–4 hours as needed. Usual maximum: 15 mg/dose
  - IV, SUB-Q continuous: Sickle cell or cancer pain 0.025 mg–2 mg/kg per hour; postoperative pain: 0.01–0.04 mg/kg per hour
- Initial adult dose:
  - 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 2–4 hours as needed
  - IV, SUB-Q continuous: 0.5–1 mg/hour
  - Epidural: 5 mg
- Maintenance adult dose:
  - Oral controlled-release usual range: 60–200 mg/day in divided doses
  - IV, SUB-Q, IM: 10 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
- Maximum dose:
  - Oral, IV, SUB-Q: No maximum dose; titrate to response
  - Epidural: 10 mg/24 hours
- Renal dosage adjustment:
  - CrCl 10–50 ml/minute: Reduce dose 25%
  - CrCl <10 ml/minute: Reduce dose 50%
  - Dialysis: Administer 50% of normal 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 Morphine
- Alcohol can disrupt the extended-release characteristic of Avinza
- CNS depressants increase sedation and dizziness

Morphine's Effect on Other Drugs
- CNS depressants: Additive effect
- MAO inhibitors and SSRIs can cause serotonin syndrome with morphine

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 doctor if pain is unrelieved
- A new prescription is required for any refill

Key Points
- Controlled substance schedule II
- Avoid use within 14 days of using an MAO inhibitor
- Contraindicated in paralytic ileus
- Avoid in patients with increase intracranial pressure such as 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
OxyContin, OxyIR, Roxicodone

Generic Name
Oxycodone

Dosage Forms
Capsules, oral liquid, oral concentrate, immediate- and controlled-release tablets

Usage
- Moderate to severe pain*

Dosing
- Initial dose: 10 mg PO every 12 hours (opioid naive)
- Maintenance dose: 20–160 mg PO every 12 hours
- Maximum dose: No maximum dose; titrate to response
- Pediatric dose: 6–12 years: 1.25 mg every 6 hours as needed

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

Oxycodone's Effect on Other Drugs
- CNS depressants: Additive effect
- MAO inhibitors and SSRIs: Serotonin syndrome

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 doctor if pain is unrelieved
- A new prescription is required for any refill

Key Points
- Controlled substance schedule II
- 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

Drug Class: Narcotic/Nonnarcotic Combinations

Introduction
Narcotic combinations are common agents prescribed for management of moderate pain. The addition of the nonopioid is commonly ibuprofen or acetaminophen, which works as a coanalgesic. 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
Narcotic component binds to opioid mu receptors altering the perception and response to pain combined with a nonnarcotic analgesic that inhibits brain prostaglandin synthesis.

Members of the Drug Class
In this section: Codeine/acetaminophen, hydrocodone/acetaminophen, hydrocodone/ibuprofen, oxycodone/acetaminophen, propoxyphene-n/acetaminophen

Others: Pseudoephedrine/hydrocodone/chlorpheniramine

Codeine/Acetaminophen

Brand Names
Tylenol 2, Tylenol 3, Tylenol 4, Tylenol with Codeine

Generic Name
Codeine/Acetaminophen

Dosage Forms
Tablets, elixir

Usage
- Moderate pain*

Dosing
- Children: 0.5–1 mg codeine/kg per dose every 4–6 hours or
  - 3–6 years: 5 ml/dose every 6 hours of elixir
  - 7–12 years: 10 ml every 6 hours of elixir
  - >12 years: 15 ml every 4 hours of elixir
- Adult: 30–60 mg codeine every 4–6 hours
- Maximum dose: 4000 mg of acetaminophen component/day (2000 mg in chronic alcoholics)
- Renal dosage adjustment:
  - CrCl 10–50 ml/minute: Reduce dose 25%
  - CrCl <10 ml/minute: Reduce dose 50%

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 effect

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 doctor if pain is unrelieved

Key Points
- Differences in individual metabolism mean that some patients will not convert codeine to its active form, necessitating the use of other agents; others may be ultra-rapid metabolizers of codeine, producing higher levels of morphine and leading to higher 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, Vicodin, Various

Generic Name
Hydrocodone/Acetaminophen

Dosage Forms
Tablets, elixir, or solution

Usage
- Moderate pain*

Dosing
- Children: <50 kg: 0.1–0.2 mg/kg per dose hydrocodone component every 4–6 hours
- Usual adult dose: 1–2 tablets every 4–6 hours or 5–10 ml elixir every 4–6 hours
- Maximum dose: 4000 mg of acetaminophen component/day (2000 mg in chronic alcoholics)

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
- Ethanol use: >3 drinks/day may increase risk of hepatotoxicity
- Isoniazid: May increase the risk hepatotoxicity

Hydrocodone/Acetaminophen's Effect on Other Drugs
- Warfarin: Increases anticoagulant effect
- CNS depressants: Additive effect

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 doctor if pain is unrelieved

Key Points
- Controlled substance schedule III
- Do not exceed acetaminophen daily dosing recommendations

Hydrocodone/Ibuprofen

Brand Names
Vicoprofen, Various

Generic Name
Hydrocodone/Ibuprofen

Dosage Forms
Tablets containing 200 mg of ibuprofen and 5, 7.5, or 10 mg of hydrocodone

Usage
- Moderate pain*

Dosing
- Usual adult dose: 1–2 tablets every 4–6 hours
- Maximum dose: 2400 mg ibuprofen (12 tablets/day)

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

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

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 doctor if pain is unrelieved

Key Points
- Controlled substance schedule III
- Do not exceed daily dosing recommendations

Oxycodone/Acetaminophen

Brand Names
Endocet, Percocet, Roxicet, Tylox

Generic Name
Oxycodone/Acetaminophen

Dosage Forms
Capsules, tablets, oral liquid; note that various dosage combinations are available

Usage
- Moderate or severe pain*

Dosing
- Initial dose: 1–2 tablets of 5 mg oxycodone/325 mg acetaminophen PO every 4–6 hours or 5–10 ml oral solution every 4–6 hours
- Maximum dose: 4000 mg acetaminophen/day (2000 mg/day in chronic alcoholics)
- Renal dosage adjustment:
  - None

Major Drug Interactions
Drugs Affecting Oxycodone/Acetaminophen
- CNS depressants: Increase sedation and dizziness
- 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

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 doctor if pain is unrelieved
- A new prescription is required for any refill

Key Points
- Multiple combinations of oxycodone/acetaminophen are available in various strengths. The most common dosage is 5 mg oxycodone/325 mg acetaminophen, which was formerly the only available strength. Prescriptions and orders for this drug must include the strength desired.
- Controlled substance schedule II
- Do not exceed acetaminophen daily dosing recommendations

Propoxyphene-n/Acetaminophen

Brand Names
Darvocet-N, Propacet, Various

Generic Name
Propoxyphene-n/Acetaminophen

Dosage Forms
Oral tablets containing 50, 65, or 100 mg of propoxyphene and 325, 500, or 650 mg of acetaminophen

Usage
- Mild to moderate pain*

Dosing
- Maintenance dose: 50–100 mg PO propoxyphene every 4 hours
- Maximum dose: 600 mg PO propoxyphene/day
- Renal dosage adjustment:
  - CrCl <10 ml/minute: Avoid use

Adverse Reactions: Most Common
- Hypotension

Absolute Contraindications
- None

Major Drug Interactions
Drugs Affecting Propoxyphene-n/Acetaminophen
- CNS depressants may increase sedation

Propoxyphene-n/Acetaminophen's Effect on Other Drugs

- Carbamazepine level may be increased due to decrease in metabolism

Counseling Points

- Avoid alcohol use
- Do not exceed the recommended dosing
- May cause drowsiness
- May cause physical or psychological dependence with prolonged use

Key Points

- Controlled substance schedule IV

Drug Class: Nonsteroidal Anti-Inflammatory Drug, 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. Their 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 still apply to it. Other agents in this class have been removed from the market.

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. COX-2 inhibitors do not appear to block COX-1 as extensively as nonselective NSAIDs, decreasing the toxicity to the GI mucosa.

Members of the Drug Class

In this section: Celecoxib
Others: None

Celecoxib

Brand Name

Celebrex

Generic Name

Celecoxib

Dosage Forms

Capsules

Usage

- Osteoarthritis*, dysmenorrhea, ankylosing spondylitis, RA*, acute pain, prevention of polyp formation in patients with familial adenomatous polyposis (FAP)

Dosing

- JRA: Children: ≥2 years: 10–25 kg, 50 mg twice daily; >25 kg, 100 mg twice daily
- Adults: 100–200 mg twice daily
- FAP: 400 mg twice daily
- Renal dosage adjustment: No specific dosing recommended; avoid in advanced renal disease
- Hepatic dosage adjustment: Reduce 50% in moderate impairment; not recommended in severe impairment

Adverse Reactions: Most Common

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

Adverse Reactions: Rare/Severe/Important

- GI perforation and bleeding, thrombosis, renal toxicity, exfoliative dermatitis, Stevens–Johnson syndrome and toxic epidermal necrolysis, fulminant hepatitis, liver failure, acute renal failure

Major Drug Interactions

Drugs Affecting Celecoxib

- Antacids: Decrease absorption of celecoxib
- Corticosteroids: Increase GI side effects
- Ethanol: Increased GI irritation
- Fluconazole can increase concentrations of celecoxib

Celecoxib's Effect on Other Drugs

- ACE inhibitors and angiotensin II receptor blockers: Decrease antihypertensive effect and increase renal toxicity
- Anticoagulants: Increase bleeding risk
- Aspirin: Increases bleeding risk; diminishes cardioprotective effect
- Cyclosporine: Increases cyclosporine levels
- Diuretics: Decreased effects
- Lithium: Increased concentrations

Counseling Points

- Be informed about signs and symptoms of GI bleeding
- Take with food if GI upset occurs
- Take as directed
- Avoid OTC products unless approved by prescriber
- Do not take with antacids

Key Points

- 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.
- May increase risk for thrombosis, stroke, and myocardial infarction
- Elderly are at increased risk for GI ulcers, CNS and renal toxicities
- Patients with hypersensitivity reactions to sulfonamides (especially nonantibiotic sulfonamides) should avoid celecoxib
- Patients with "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.
- 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, the elderly or debilitated patients.

Drug Class: Nonsteroidal Anti-Inflammatory Drugs

Introduction

Nonsteroidal anti-inflammatory drugs are commonly used for mild pain symptoms. They possess both 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, and they are listed here.

Mechanism of Action of the Drug Class

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

Members of the Drug Class

In this section: Aspirin, diclofenac, etodolac, ibuprofen, indomethacin, meloxicam, nabumetone, naproxen

Others: Diflunisal, fenoprofen, flurbiprofen, ketoprofen, ketorolac, meclofenamate, mefenamic acid, oxaprozin, piroxicam, sulindac, tolmetin

Major Drug Interactions for the Drug Class

Drugs Affecting NSAIDs

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

NSAIDs' Effect on Other Drugs

- ACE inhibitors and angiotensin II receptor blockers: Decrease antihypertensive effect
- Anticoagulants: Increase bleeding risk
- Diuretics: Diminish diuretic effect
- Heparin: Increases anticoagulant effect
- Warfarin: Enhances anticoagulant effect
- Lithium: Increased concentrations, possible toxicity

Adverse Reactions for the Drug Class: Most Common

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

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

Counseling Points for the Drug Class

- Be aware of the signs and symptoms of GI bleeding
- Take with food if GI upset occurs
- Do not take with antacids

Key Points for the Drug Class

- Use with caution in patients with fluid retention, congestive heart failure, renal insufficiency, or hypertension. They are not contraindicated in these disease states but may worsen them in some situations.
- Use of NSAIDs can compromise existing renal function. Renal toxicity can 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.
- May increase risk for thrombosis, stroke, and myocardial infarction
- Elderly patients are at increased risk for GI ulcers, CNS and renal toxicities
- Patients with "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.
- 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, the elderly or debilitated patients. The concurrent use of proton pump inhibitors or histamine-2 antagonists may reduce the risk of GI ulcers in high-risk patients.

Aspirin

Brand Names
Bayer, Excedrin, Various

Generic Name
Aspirin

Dosage Forms
Enteric coated, buffered, chewable, and controlled-release tablets; gum, suppository

Usage
- Treatment of mild–moderate pain*, inflammation, and fever
- Prevention and treatment of MI*, acute ischemic stroke*, and transient ischemic episodes*
- Management of RA, rheumatic fever, osteoarthritis, and gout (high dose)
- Adjunctive therapy in revascularization procedures (CABG*, PTCA, carotid endarterectomy*), and stent implantation*

Dosing
- Adults:
  - Antiplatelet indications: 50–325 mg daily
  - Pain and inflammation:
    - Oral: 325–650 mg every 4–6 hours up to 4 g/day
    - Rectal: 300–600 mg every 4–6 hours up to 4 g/day
- Pediatrics:
  - Analgesic and antipyretic: Oral, rectal: 10–15 mg/kg/dose every 4–6 hours, up to a total of 4 g/day
  - Anti-inflammatory: Oral: Initial: 60–90 mg/kg per day in divided doses; usual maintenance: 80–100 mg/kg per day divided every 6–8 hours

Adverse Reactions: Rare/Severe/Important
- In addition to the NSAID adverse effects just listed, Reye's syndrome

Major Drug Interactions
Drugs Affecting Aspirin
- Ginkgo biloba: Increases antiplatelet effect
- Other NSAIDs: Diminish cardioprotective effects

Aspirin's Effect on Other Drugs
- Varicella vaccine: Increases risk of Reye's syndrome

Key Points
- Do not use in children for viral infections due to the potential for Reye's syndrome, a rare but life-threatening disorder associated with aspirin use during viral infections
- Contraindicated during pregnancy and in patients with bleeding disorders

Diclofenac

Brand Names
Voltaren, Voltaren-XR, Cataflam, Flector

Generic Name
Diclofenac

Dosage Forms
Tablets, extended-release tablets, transdermal patches, topical gel, ophthalmic solution

Usage
- Acute treatment for mild to moderate pain*, dysmenorrhea*, osteoarthritis*, RA*, ankylosing spondylitis, postoperative inflammation following eye surgery, actinic keratosis

Dosing
- Initial dose: 50 mg three times daily
- Maintenance dose: 150–200 mg daily in divided doses
- Maximum dose: 200 mg daily
- Topical gel: 2–4 g to affected area four times daily
- Topical patch: 1 patch daily to painful site
- Renal dosage adjustment:
  - Use with caution in patients with renal impairment

Etodolac

Brand Name
Lodine

Generic Name
Etodolac

Dosage Forms
Tablets, capsules, extended-release tablets

Usage
- Acute treatment for mild to moderate pain*, osteoarthritis*, RA*

Dosing
- Acute pain: 200–400 mg every 6–8 hours as needed, maximum dose of 1000 mg/day; extended-release tablet dosing needed
- Children (6–16 years) for JRA: 400–1000 mg daily depending on weight using extended-release product
- Renal dosage adjustment:
  - Use with caution in patients with severe impairment; no adjustment for mild–moderate impairment

Ibuprofen

Brand Names
Motrin, Cal dolor, NeoProfen; OTC preparations available as Advil, Motrin, Excedrin IB, Haltran, Ibuprin, Midol 200, Nuprin, Pamprin IB, Trendar, Uni-Pro

Generic Name
Ibuprofen

Dosage Forms
Tablets, chewable tablets, caplets, oral infant drops, oral suspension, injection

Usage
- Acute treatment for mild to moderate pain, acute treatment for gout, osteoarthritis, RA, antipyretic, dysmenorrhea, patent ductus arteriosus, ankylosing spondylitis, cystic fibrosis
- Common uses: Mild to moderate pain and fever

Dosing
- Adults:
  - Initial dose: 200–800 mg three to four times daily
  - Maximum dose: 3200 mg daily
- Children:
  - Antipyretic, analgesic: 5–10 mg/kg/dose every 6–8 hours up to 40 mg/kg per day
  - JRA: 30–50 mg/kg per day
  - Cystic fibrosis: Maintain serum concentration 50–100 µg/ml
  - Patent ductus arteriosus (ibuprofen lysine): 10 mg/kg followed by two doses of 5 mg/kg at 24 and 48 hours

Adverse Reactions: Most Common
- Infant injection: Skin irritation, intraventricular hemorrhage, hypocalcemia, hypoglycemia, anemia, sepsis, apnea

Adverse Reactions: Rare/Severe/Important
- Injection: Electrolyte imbalances, hemorrhage

Indomethacin

Brand Names
Indocin, Indocin SR

Generic Name
Indomethacin

Dosage Forms
Capsules, extended-release capsules, injection, suspension, suppository

Usage
- Pain and inflammation associated with rheumatoid disorders, moderate to severe osteoarthritis*, acute gout*, acute bursitis/tendonitis, ankylosing spondylitis, patent ductus arteriosus*

Dosing
- Initial: 25–50 mg 2–3 times daily; sustained-release capsules should be given one to two times daily; maximum dose 200 mg daily
- Pediatric: Patent ductus arteriosus
  - IV: 0.2 mg/kg followed by two doses depending on postnatal age

Adverse Reactions: Most Common
- Infant injection: Skin irritation, intraventricular hemorrhage, hypocalcemia, hypoglycemia, anemia, sepsis, apnea

Adverse Reactions: Rare/Severe/Important
- Injection: Electrolyte imbalances, hemorrhage

Meloxicam

Brand Name
Mobic

Generic Name
Meloxicam

Dosage Forms
Tablets, oral suspension

Usage
- Osteoarthritis*, RA*, JRA

Dosing
- Adults: 7.5 mg daily up to 15 mg daily
- Children: 0.125 mg/kg per day; maximum dose 7.5 mg daily
- Renal dosage adjustment:
  - Use with caution in patients with severe impairment; no adjustment for mild to moderate impairment

Nabumetone

Brand Name
Relafen

Generic Name
Nabumetone

Dosage Forms
Tablets

Usage
- Osteoarthritis* and RA*

Dosing
- 1000 mg/day; maximum 2000 mg daily
- Renal dosage adjustment:
  - Moderate impairment CrCl 30–49 ml/minute: initial 750 mg up to 1500 mg/day
  - Severe impairment CrCl <30 ml/minute initial 500 mg up to 1000 mg/day

Naproxen

Brand Names
Naprosyn, Anaprox, Aleve (OTC)

Generic Name
Naproxen

Dosage Forms
Tablets, capsules, controlled-release tablets, enteric-coated tablets, suspension

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

Dosing
- 250–500 mg every 8–12 hours

Review Questions

1. Which of the following are the most likely potential side effects of Tylenol 3?
   A. Constipation, nausea, itching
   B. Diarrhea, nausea, dizziness, myalgias
   C. Diarrhea, nausea, renal impairment
   D. Myalgias, constipation, sedation

2. Dilaudid is classified as which of the following?
   A. Schedule II controlled substance
   B. Schedule III controlled substance
   C. Schedule IV controlled substance
   D. Schedule V controlled substance

3. Which of the following is true regarding OxyContin?
   A. It can be crushed or chewed if the patient is unable to swallow the tablets.
   B. It is a short-acting agent and should be dosed every 4–6 hours.
   C. It is a short-acting analgesic and should be given on an as-needed basis.
   D. It is a long-acting analgesic and should be dosed every 12 hours.

4. Which of the following is an uncommon potential side effect from oral morphine use?
   A. Constipation
   B. Nausea
   C. Pruritus
   D. Respiratory depression

5. Which of the following NSAIDs is selective for COX-2 and has a reduced incidence of GI ulcers?
   A. Celebrex
   B. Etodolac
   C. Mobic
   D. Naproxen

6. Which of the following is a potential side effect from methadone?
   A. QTc prolongation cardiac arrhythmias
   B. Renal impairment
   C. Reye's syndrome
   D. Steven–Johnson syndrome

7. Fentanyl is available in all the following dosage forms except
   A. Buccal tablet
   B. Injection
   C. Oral tablet
   D. Transdermal patch

8. Which of the following is an indication for using Fioricet?
   A. Headache
   B. Neuropathic pain
   C. Osteoarthritis
   D. Rheumatoid arthritis

9. Which of the following drugs can interact with Ultram, potentially causing a seizure?
   A. Acetaminophen
   B. Ibuprofen
   C. Phenytoin
   D. Tricyclic antidepressants

10. All of the following are potential side effects of NSAIDs except
    A. Agitation
    B. Cardiovascular events
    C. GI ulcers
    D. Peripheral edema

11. Which of the following is frequently used in the treatment of opioid addiction?
    A. Codeine
    B. Methadone
    C. Morphine
    D. Naproxen

12. All of the following are indications to use aspirin except
    A. Analgesic for headache
    B. Antipyretic for viral infections in children
    C. Kawasaki disease
    D. Postmyocardial infarction

13. Excedrin has the potential to interact with all of the following except
    A. Butalbital
    B. Ginkgo biloba
    C. Heparin
    D. Warfarin

14. Which of the following products could lead to hepatic failure if dosing exceeds recommended daily dosing?
    A. Celebrex
    B. Methadose
    C. Ultram
    D. Vicodin

15. Which of the following is used to treat patent ductus arteriosus in neonates?
    A. Celecoxib
    B. Indomethacin
    C. Meloxicam
    D. Nabumetone