CHAPTER 1

Analgesics

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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, as well as antipyretics, 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.

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. 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 caffeine; butalbital with caffeine, acetaminophen, and codeine

◉ Acetaminophen

Brand Names

Tylenol, Paracetamol, Ofirmev (injectable), various others

Generic Name

Acetaminophen

OTC

Injection: Rx only

Dosage Forms

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

Usage

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

Pregnancy Category B (Oral) and C (Injection)

Dosing

- Usual dose:
  - 500–650 mg PO every 4–6 hours as needed
  - Maximum adult dose: 4 g/day and 3 g/day for chronic use
- IV:
  - < 50 kg: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours
    - Maximum single dose: 750 mg
    - Maximum daily dose: 75 mg/kg/day
  - > 50 kg: 650 mg every 4 hours or 1,000 mg every 6 hours
    - Maximum single dose: 1,000 mg
    - Maximum daily dose: 4 g/day
- Children:
  - Age > 12 years: Refer to adult dosing
  - Oral:
    - 10–15 mg/kg per dose every 4–6 hours as needed
    - Do not exceed 5 doses in 24 hours
  - IV:
    - 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours
    - Maximum single dose: 15 mg/kg
    - Maximum daily dose: 75 mg/kg
  - Rectal: < 12 years 10–20 mg/kg every 4–6 hours as needed

* Throughout the text, an asterisk (*) is used to indicate the most common uses of a drug.

- Renal impairment:
  - CrCl 10–50 mL/min: administer every 6 hours
  - CrCl < 10 mL/min: administer every 8 hours
- Hepatic impairment: Limit to 2 g/day in chronic alcoholics and avoid chronic use

Adverse Reactions: Most Common

Nontoxic at therapeutic doses

Adverse Reactions: Rare/Severe/Important

Hepatotoxicity with excessive dosing

Major Drug Interactions

Drugs Affecting Acetaminophen

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

Acetaminophen's Effect on Other Drugs

Warfarin: Increased anticoagulant effect

Contraindications

Hypersensitivity to acetaminophen or any component of the formulation; severe hepatic impairment or severe active liver disease

Essential Monitoring Parameters

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

Counseling Points

- Report unresolved pain or fevers to your healthcare provider
- Use weight-based dosing in children
- Adults: Do not exceed 4 g/day; less than 3g/day for chronic dosing
- Shake suspension well before pouring
- Extended-release products must be swallowed whole, not chewed or crushed

Key Points

- Adherence to maximum daily dose recommendations is important to avoid hepatotoxicity
- Many OTC cold and pain products and opioid analgesic combinations contain acetaminophen, and patients should be warned to avoid inadvertently overdosing on acetaminophen by taking them in excessive combinations.
- Careful consideration should be taken when measuring out a pediatric dose from a liquid formulation to ensure correct dosing
- Acetaminophen is the preferred analgesic during pregnancy and breastfeeding

Butalbital with Caffeine and Acetaminophen

Brand Names

Fioricet, Zebutal, Dolgic Plus

Generic Names

Butalbital, acetaminophen, caffeine

Rx Only

Class III controlled substance

Dosage Forms

Tablet, capsule, oral liquid

Usage

Relief of tension or muscle contraction headaches*

Pregnancy Category C

Dosing

- Initial:
  - 1–2 tablets or capsules (or 15–30 mL solution) every 4 hours
  - Do not to exceed 6 tablets or capsules (or 180 mL solution) daily
- Renal dosage adjustment: Caution using in severe impairment
- Hepatic dosage adjustment: Caution using in severe impairment

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 of hepatotoxicity

Butalbital with Caffeine and Acetaminophen's Effect on Other Drugs

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

Contraindications
Hypersensitivity to butalbital, acetaminophen, caffeine, or any component of the formulation; porphyria

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

Key Point
Many OTC cold and pain products contain acetaminophen; increased risk of hepatotoxicity when taken with butalbital, acetaminophen, and caffeine combinations

ANALGESICS, NARCOTICS

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.

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

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

◉ Buprenorphine

Brand Names
Buprenex, Butrans, Subutex

Generic Name
Buprenorphine

Rx Only
Class III controlled substance

Dosage Forms
Injection, transdermal patch, sublingual tablet

Usage
Moderate to severe pain,* opioid dependence,* opioid withdrawal in heroin-dependent hospitalized patients

Pregnancy Category C

Dosing
- Usual dose: 0.15–0.6 mg every 4–8 hours as needed
- Acute pain: 0.3 mg IM or IV every 6–8 hours as needed
- Chronic pain: transdermal patch; opioid-naïve: Initial 5 μg/hour applied once every 7 days; may titrate with a minimum interval of 72 hours up to a maximum patch dose of 20 μg/hr applied once every 7 days. Patients receiving daily dose of 30–80 mg of oral morphine equivalent may be initiated at 10 μg/hour applied once every 7 days.
- Opioid dependence: Sublingual tablets; day 1: 8 mg; 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 6–12 hours

Adverse Reactions: Most Common
Sedation, hypotension, dizziness, nausea, vomiting, headache, respiratory depression (IV), constipation, application site rash (patch)

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

Contraindications to the transdermal patch: Management of mild, acute, or intermittent pain; management of pain requiring short-term opioid analgesia; management of postoperative pain

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

- The combination of buprenorphine and naloxone is preferred over buprenorphine monotherapy for maintenance treatment of opioid dependence
- 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 in the REMS program to prescribe the tablets and transdermal patch
- Transdermal patch should not be used for postoperative or acute pain
- Avoid use if suspected paralytic ileus
- Avoid use within 14 days of a MAO inhibitor

◉ Fentanyl

Brand Names

Actiq, Duragesic, Fentora, Sublimaze, Onsolis, Lazanda

Generic Name

Fentanyl

Rx Only

Class II controlled substance

Dosage Forms

Transdermal patch, buccal tablets, buccal film, buccal lozenge, nasal spray, sublingual spray, injection

Usage

Severe pain*

Pregnancy Category C

Dosing

- Initial dose:
  - Transdermal patch: 12.5–25 µg/hour every 72 hours
  - Buccal: 200 µg every 3 hours as needed
  - IV:
    - Single dose: 25–100 µg
    - Infusion: 1 µg/kg per hour
- Maintenance dose: Titrate to response; usual basal rate < 50 µg/hr IV
- Maximum dose: Usually 4 patches for the transdermal system (limited by skin surface area); no maximum dose based on efficacy
- Epidural:
  - Single dose: 25–100 µg
  - Continuous infusion: 25–100 µg/hour
- Intrathecal: 5–25 µg/dose
- Nasal and sublingual spray: Initial 100 µg/dose/spray

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
- Avoid direct heat on the 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

- Fentanyl has a shorter half-life than other opiates in its class
- Avoid use within 14 days of using an MAO inhibitor
- 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
- 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 or for acute and postoperative pain
- Use preservative-free solution for epidural and intrathecal use
- All physicians prescribing the buccal formulations must be registered in REMS program.
- The transmucosal products have specific disposal instructions.

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

Moderate to severe pain,* antitussive

Pregnancy Category C

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
  - Oral, IV, SUB-Q: No maximum dose; titrate to response
  - Extended-release: 8–64 mg PO every 24 hours in opioid-tolerant patients only

Adverse Reactions: Most Common

Constipation, nausea, vomiting, sedation, dizziness, xerostomia, pruritus (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 healthcare provider if pain is unrelieved
- The extended-release tablets must be swallowed whole
- A new prescription is required for any refill

Key Points

- 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, dispersible tablet, injection, oral solution

Usage

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

Pregnancy Category C

Dosing

- Severe pain:
  - Initial dose:
    - Oral: 5 mg every 6–8 hours
    - IV: 2.5–10 mg 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: If CrCl < 10 mL/min, 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
- 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

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

- 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.
- 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

Astramorph, Avinza, Kadian, MS Contin, Oramorph, Roxanol, various others

Generic Name

Morphine

Rx Only

Class II controlled substance

Dosage Forms

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

Usage

Moderate to severe pain*

Pregnancy Category C

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: 0.025–2 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/min: Reduce dose 25%
  - CrCl < 10 mL/min: 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: May cause serotonin syndrome
- SSRIs: May cause serotonin syndrome

Contraindications

MAO inhibitor use (concurrent or within 14 days)

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

- Avoid use within 14 days of using an MAO inhibitor
- Contraindicated in paralytic ileus
- Avoid in patients with increase 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

OxyContin, OxyIR, Roxicodone

Generic Name

Oxycodone

Rx Only

Class II controlled substance

Dosage Forms

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

Usage

Moderate to severe pain*

Pregnancy Category C

Dosing

- Initial dose:
  - 5–15 mg PO every 4–6 hours as needed
  - 10 mg extended-release PO: Every 12 hours (opioid naive)
- Maintenance extended-release dose: 20–160 mg PO every 12 hours
- Maximum dose: No maximum dose; titrate to response
- Pediatric dose (6–12 years): 1.25 mg PO 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: May cause serotonin syndrome
- SSRIs: May cause 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 healthcare provider if pain is unrelieved
- A new prescription is required for any refill

Key Points

- 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

Tablet, extended-release tablet

Usage

Moderate to severe pain*

Pregnancy Category C

Dosing

- Acute pain: 50–100 mg every 4–6 hours as needed; maximum daily dose on day 1 of 700 mg/day and 600 mg/day on subsequent days
- Chronic pain: Extended-release 50 mg PO every 12 hours initially, up to a maximum of 500 mg/day; may titrate every 3 days
- Moderate hepatic impairment: Decrease immediate-release dosing to 50 mg every 8 hours or extended-release to 50 mg every 24 hours
- Severe renal impairment: Use not recommended
- Severe hepatic impairment: 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

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

- 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, Rybix ODT, Ultram, Ultram ER, Ultracet

Generic Name

Tramadol

Rx Only

Dosage Forms

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

Usage

Moderate* to severe pain, neuropathic pain

Pregnancy Category C

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 immediate-release PO every 12 hours
- Renal dosage adjustment: 50–100 mg immediate-release PO every 12 hours (maximum: 200 mg/day)

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
- 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

- Extended-release tablets must be swallowed whole
- 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
- It is *not* a controlled substance
- 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 nonopioid is most 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

The narcotic component binds to opioid μ-receptors, altering the perception and response to pain. The non-narcotic analgesic inhibits brain prostaglandin synthesis.

Contraindications of the Drug Class

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

Members of the Drug Class

In this section: Codeine/acetaminophen, hydrocodone/acetaminophen, hydrocodone/ibuprofen, 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

Usage

Mild to moderate pain,* antitussive

Pregnancy Category C

Dosing

- Children: 0.5–1 mg codeine/kg per dose every 4–6 hours *or*
  - 3–6 years: 5 mL 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:
  - Antitussive: 15–30 mg codeine every 4–6 hours
  - Pain: 30–60 mg codeine every 4–6 hours
  - Maximum dose: 4,000 mg of acetaminophen component/day (2,000 mg in chronic alcoholics)
- Renal dosage adjustment:
  - CrCl 10–50 mL/min: Reduce dose 25%
  - CrCl < 10 mL/min: Reduce dose 50%
- Hepatic dosage adjustment: Limit acetaminophen component to < 2 g/day and avoid in cirrhosis patients

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

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

- 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, Zydone, various others

Generic Name

Hydrocodone/acetaminophen

Rx Only

Class III controlled substance

Dosage Forms

Tablet, capsule, oral solution

Usage

Moderate pain*

Pregnancy Category C

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: 4,000 mg of acetaminophen component/day (2,000 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 healthcare provider if pain is unrelieved

Key Points
- 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
Moderate pain*

Pregnancy Category C

Dosing
- Usual adult dose: 1 tablet every 4–6 hours
- Maximum dose: 5 tablets per 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

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

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
- Schedule III controlled substance
- Do not exceed daily dosing recommendations

Oxycodone/Acetaminophen

Brand Names
Endocet, Percocet, Roxicet, Tylox

Generic Name
Oxycodone/acetaminophen

Rx Only
Class II controlled substance

Dosage Forms
Capsule, caplet, tablet, oral liquid

Usage
Moderate or severe pain*

Dosing
- Initial dose:
  - Tablets: 1–2 tablets every 4–6 hours
  - Oral solution: 5–10 mL oral solution every 4–6 hours
- Maximum dose: 3,000 mg acetaminophen/day (2,000 mg/day in chronic alcoholics)

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

Key Points
- 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, SELECTIVE COX-2 INHIBITORS

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.

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 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,* ankylosing spondylitis, juvenile idiopathic arthritis (JIA), and rheumatoid arthritis*; management of acute pain; treatment of primary dysmenorrhea

Pregnancy Category C (Prior to 30 Weeks Gestation) and D (≥ 30 Weeks Gestation)

Dosing

- Osteoarthritis: 200 mg/day PO as a single dose or in divided doses twice daily
- 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
  - Canadian labeling: Recommended maximum dose of 200 mg/day
- Rheumatoid arthritis: 100–200 mg PO twice daily
- Acute pain or primary dysmenorrhea:
  - Initial dose: 400 mg, followed by an additional 200 mg if needed on day 1
  - Maintenance dose: 200 mg twice daily as needed
- Renal dosage adjustment: 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 ulcers, bleeding, and perforation; thrombosis, including MI and stroke; renal toxicity; exfoliative dermatitis; Stevens-Johnson syndrome; 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

Contraindications

Hypersensitivity to celecoxib, 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

- 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.
- Black box warning: Increased risk for thrombosis, stroke, and myocardial infarction
- Elderly are at increased risk for GI ulcers, CNS effects, 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; and the elderly or debilitated patients.
- Celecoxib does not inhibit platelets or prolong bleeding time

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) 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. Agent-specific characteristics are listed with the individual agents.

Mechanism of Action of the Drug Class

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

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

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: Decrease antihypertensive effect
- Anticoagulants: Increase bleeding risk
- Antiplatelet therapy: Increases bleeding risk
- Beta blockers: Diminish effect
- Digoxin: Increase level
- Diuretics: Diminish diuretic effect
- Heparin: Increases anticoagulant effect
- Warfarin: Enhances anticoagulant effect
- Lithium: Increased concentrations, possible toxicity

Contraindications for the Drug Class

Hypersensitivity to aspirin or NSAIDS, peptic ulcer disease, perioperative pain with coronary artery bypass graft (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

- Use with caution in patients with fluid retention, congestive heart failure, renal insufficiency, or hypertension. They are not contraindicated in these disease states, but they 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 effects, 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.

Members of the Drug Class

In this section: Aspirin, diclofenac, etodolac, ibuprofen, indomethacin, ketorolac, meloxicam, nabumetone, naproxen
Others: Diflunisal, fenoprofen, flurbiprofen, ketoprofen meclofenamate, mefenamic acid, 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; gum; suppository

Usage

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

Pregnancy Category

No formal category, but it is contraindicated except for low doses

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:
    - Initial: 60–90 mg/kg per day PO in divided doses
    - Maintenance: 80–100 mg/kg per day PO in divided doses every 6–8 hours
- 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: Increases antiplatelet effect
- Other NSAIDs: Increase bleeding risk

Aspirin's Effect on Other Drugs

- ACE inhibitors: Diminish the antihypertensive effect
- Anticoagulants: Increase bleeding risk

Contraindications

Hypersensitivity to salicylates, other NSAIDs, or any component of the formulation; nasal polyps; 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

Counseling Points

- High-dose aspirin should only be used 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
- Contraindicated during pregnancy and in patients with bleeding disorders
- Aspirin therapy should be stopped 1 week prior to surgery to reduce bleeding risk unless otherwise indicated by physician

◉ Diclofenac

Brand Names

Flector, Pennsaid, Solaraze, Voltaren

Generic Name

Diclofenac

Rx Only

Dosage Forms
Capsule, tablet, delayed-release enteric tablet, extended-release tablet, topical gel, topical solution, transdermal patch, ophthalmic solution

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, or topical gel 1%, topical solution, topical patch: Category C
- Oral or topical solution ≥ 30 weeks gestation: Category D

Dosing
- Analgesia: 50 mg PO three times daily
- Primary dysmenorrhea: 150–200 mg PO daily in divided doses
- Rheumatoid arthritis and osteoarthritis:
  - 150–200 mg/day in divided doses
  - Extended-release: 100–200 mg 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
  - Lower extremities: 4 g to affected area four times daily
- Topical patch: 1 patch daily to painful site
- Topical solution: Apply 40 drops four times daily to each affected knee
- Cataract surgery: Instill 1 drop ophthalmic solution into affected eye four times daily beginning 24 hours after cataract surgery and continuing for 2 weeks
- Corneal refractive surgery: Instill 1–2 drops 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

Contraindications
Hypersensitivity to bovine protein (capsule formulation only)

Etodolac
Brand Name
Lodine

Generic Name
Etodolac

Rx Only

Dosage Forms
Tablet, capsule, extended-release tablet

Usage
Acute treatment for mild to moderate pain,* osteoarthritis,* rheumatoid arthritis*

Pregnancy Category C

Dosing
- Acute pain: 200–400 mg every 6–8 hours as needed, maximum dose of 1,000 mg/day
- Rheumatoid arthritis, osteoarthritis:
  - Immediate-release formulation: 400 mg twice daily *or* 300 mg two to three daily *or* 500 mg twice daily (doses > 1,000 mg/day have not been evaluated)
  - Extended-release formulation: 400–1,000 mg once daily
- Children (6–16 years) for juvenile rheumatoid arthritis: 400–1,000 mg daily depending on weight using extended-release product
- Dosing in renal impairment: Avoid use in severe impairment

Counseling Points
- 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

Ibuprofen
Brand Names
Motrin, Caldolor, NeoProfen, Advil, Motrin, Excedrin IB, Haltran, Ibuprin, Midol 200, Nuprin, Pamprin IB, Trendar, Uni-Pro

Generic Name
Ibuprofen

OTC and Rx (Injection)

Dosage Forms
Tablet, chewable tablet, caplet, oral infant drops, oral suspension, injection

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

Pregnancy Category C
Pregnancy category D after ≥ 30 weeks gestation

Dosing

- Adults:
  - Inflammatory disease: 400–800 mg PO three to four times a day; maximum 3.2 g/day
  - Analgesia/pain/fever/dysmenorrhea: 200–400 mg PO every 4–6 hours (maximum daily dose: 1.2 g, unless directed by physician; under physician supervision, daily doses ≤ 2.4 g may be used)
  - Analgesic IV: 400–800 mg every 6 hours as needed (maximum: 3.2 g/day)
  - Antipyretic IV: Initial dose of 400 mg, then every 4–6 hours or 100–200 mg every 4 hours as needed (maximum: 3.2 g/day)
  - Analgesic, antipyretic OTC labeling: 200 mg PO every 4–6 hours as needed (maximum: 1,200 mg/24 hours)
  - Migraine OTC labeling: 2 capsules or tablets at the onset of symptoms (maximum: 400 mg/24 hours)
- Children:
  - Antipyretic for ages 6 months to 12 years:
    - Temperature < 102.5°F (39°C): 5 mg/kg PO
    - Temperature > 102.5°F (39°C): 10 mg/kg PO given every 6–8 hours
    - Maximum daily dose: 40 mg/kg/day
  - Juvenile idiopathic arthritis (JIA): 30–50 mg/kg every 24 hours PO divided every 8 hours; start at lower end of dosing range and titrate upward (maximum: 2.4 g/day)
  - Analgesic: 4–10 mg/kg PO every 6–8 hours
  - Chronic (> 4 years) cystic fibrosis (unlabeled use): Twice-daily PO dosing adjusted to maintain serum concentration of 50–100 μg/mL has been associated with slowing of disease progression in younger patients with mild lung disease
  - Patent ductus arteriosus: IV ibuprofen lysine (NeoProfen): Infants between 500–1,500 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.

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 Point

Patients should be well hydrated prior to the administration of IV ibuprofen

Indomethacin

Brand Names

Indocin, Indocin SR

Generic Name

Indomethacin

Rx Only

Dosage Forms

Capsule, extended-release capsule, 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*

Pregnancy Category C

Dosing

- Initial: 25–50 mg two to three times daily; sustained-release capsules should be given one to two times daily; maximum dose 200 mg daily
- Inflammatory/rheumatoid disorders (use lowest effective dose):
  - Oral, rectal: 25–50 mg/dose two to three times a day; maximum dose is 200 mg/day
  - Extended-release capsule: Should be given once or twice 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 three to four divided doses
  - Extended-release: One to two divided doses
  - Usual treatment: 7–14 days
- Acute gouty arthritis, oral, rectal: 50 mg three times daily until pain is tolerable, then reduce dose; usual treatment < 3–5 days
- Patent ductus arteriosus (pediatric-only indication): 0.2 mg/kg IV 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

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: C
- Nasal after ≥ 30 weeks gestation: 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 every 4–6 hours; do not exceed 40 mg/day; oral dosing is intended to be a continuation of IM or IV therapy only
  - Geriatric:
    - 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)
- Nasal spray:
  - One spray in each nostril every 6–8 hours up to four times daily
  - Adults < 50 kg or ≥ 65 years of age: One spray in one nostril up to four times daily
- Seasonal allergic conjunctivitis (relief of ocular itching): Instill 1 drop (0.25 mg) of ophthalmic solution four times daily
- Inflammation following cataract extraction: Instill 1 drop (0.25 mg) ophthalmic solution to affected eye(s) four times daily beginning 24 hours after surgery; continue for 2 weeks
- Pain following corneal refractive surgery: Instill 1 drop of ophthalmic solution four times daily as needed to affected eye for up to 4 days

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

Key Points
- Use lowest effective dose and limit use to 5 days to decrease the risk of ulcers
- Prolonged use may lead to renal toxicity

Meloxicam

Brand Name
Mobic

Generic Name
Meloxicam

Rx Only

Dosage Forms
Tablet, oral suspension

Usage
Osteoarthritis,* rheumatoid arthritis,* juvenile rheumatoid arthritis

Pregnancy Category C
Pregnancy category D ≥ 30 weeks gestation

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 not recommended in patients with severe impairment
  - No adjustment for mild to moderate impairment

Nabumetone

Brand Name
Relafen

Generic Name
Nabumetone

Rx Only

Dosage Form
Tablet

Usage
Osteoarthritis,* rheumatoid arthritis*

Pregnancy Category C

Dosing
- 1,000 mg/day; maximum 2,000 mg daily
- Renal dosage adjustment:
  - Moderate impairment of CrCl 30–49 mL/min: Initial 750 mg up to 1,500 mg/day
  - Severe impairment of CrCl < 30 mL/min: Initial 500 mg up to 1,000 mg/day

Naproxen

Brand Names
Aleve, Anaprox, Midol, Naprosyn, Pamprin

Generic Name
Naproxen

OTC and Rx

Dosage Forms
Tablet, capsule, controlled-release tablet, enteric-coated tablet, gelcap, suspension

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

Pregnancy Category C

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: 1,250 mg in 24 hours
- Pain (mild to moderate), dysmenorrhea, acute tendonitis, bursitis: Initial 500 mg PO, then 250 mg every 6–8 hours; maximum: 1,250 mg/day naproxen base
- 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 limited time period
- OTC labeling for pain/fever: 200 mg naproxen base every 8–12 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

REVIEW QUESTIONS

1. Which of the following agents can be used as an analgesic and antipyretic but does not possess any anti-inflammatory activity?
   a. Acetaminophen
   b. Butalbital
   c. Codeine
   d. Meloxicam

2. Acetaminophen is available in which of the following dosage forms?
   a. Tablet, liquid
   b. Tablet, liquid, suppository
   c. Tablet, liquid, gelcap, suppository, extended-release
   d. Tablet, liquid, gelcap, suppository, extended-release, injection

3. Which of the following is the analgesic of choice during pregnancy?
   a. Ibuprofen
   b. Codeine
   c. Acetaminophen
   d. Butorphanol

4. Acetaminophen has a maximum daily dosing because of which of the following adverse effects?
   a. Gastrointestinal bleeding
   b. Renal toxicity
   c. Hepatic toxicity
   d. Neurotoxicity

5. Fioricet, a combination product used for headaches, contains which of the following?
   a. Butalbital
   b. Butalbital, aspirin
   c. Butalbital, caffeine
   d. Butalbital, caffeine, acetaminophen

6. Which of the following is the maximum dose of Fioricet per day?
   a. 4 tabs
   b. 6 tabs
   c. 8 tabs
   d. 10 tabs

7. Which of the following is both a μ-agonist and an inhibitor of norepinephrine uptake?
   a. Tapentadol
   b. Butorphanol
   c. Buprenorphine
   d. Methadone

8. Which of the following is true regarding buprenorphine?
   a. It is a Class II controlled substance.
   b. It is only available as oral tablets.
   c. It is indicated for moderate to severe pain and opioid dependence.
   d. It is safe and effective for pregnant patients.

9. Butrans should be limited to a maximum dose of 20 μg/hr because of the risk of which of the following?
   a. Sedation
   b. Respiratory depression
   c. QTc prolongation
   d. Constipation

10. Which of the following would be an appropriate use of fentanyl patches?
    a. Acute postoperative pain
    b. Sickle cell crisis
    c. Chronic cancer pain
    d. Labor and delivery pain

11. Which of the following is true regarding fentanyl?
    a. Short-acting buccal fentanyl can only be prescribed by physicians registered in the REMS program.
    b. It is available only in transdermal and injectable forms.
    c. It is a Class III controlled substance.
    d. It has a longer half-life than other narcotics in its class.

12. Which of the following would be an appropriate dose and frequency for fentanyl transdermal?
    a. 25 μg/hr patch changed daily
    b. 50 μg/hr patch changed every 48 hours
    c. 75 μg/hr patch changed every 72 hours
    d. 10 μg/hr patch changed every 48 hours

13. Which of the following is a brand name of a buccal fentanyl product?
    a. Onsolis
    b. Duragesic
    c. Sublimaze
    d. Lazanda

14. Which of the following would an appropriate starting dose of hydromorphone in an adult?
    a. 20 mg PO every 4 hours as needed
    b. 4 mg PO every 4 hours as needed
    c. 64 mg PO daily
    d. 10 mg/hr IV continuous infusion

15. Which of the following is true of methadone?
    a. Any physician can prescribe methadone for opiate addiction.
    b. Methadone has a short half-life.
    c. Methadone is a Schedule II narcotic.
    d. Methadone should not be used for pain.

16. Which of the following monitoring parameters are recommended for methadone?
    a. ECG
    b. Echocardiogram
    c. EEG
    d. EMG

17. Which of the following is true regarding morphine?
    a. It requires no dose adjustment for severe renal impairment.
    b. It is only available in oral and injectable forms.
    c. It can cause constipation, dizziness, and itching.
    d. The extended-release products are recommended for acute pain.

18. Which of the following is a common brand name of extended-release oxycodone?
    a. Roxanol
    b. Opana
    c. OxyContin
    d. Percocet

19. Which of the following is true of oxycodone?
    a. It is a Class III controlled substance.
    b. It is pregnancy category D.
    c. It is available as an injection.
    d. It can cause psychological dependence with prolonged use.

20. Ketorolac is available in which of the following dosage forms?
    a. Tablet, capsule, injection, nasal spray
    b. Tablet, injection, nasal spray
    c. Tablet, injection, nasal spray, ophthalmic solution
    d. Tablet, capsule, injection, nasal spray, ophthalmic solution

21. Which of the following includes all the available dosage forms for tramadol?
    a. Immediate-release tablet
    b. Immediate-release tablet, extended-release tablet
    c. Immediate-release tablet, extended-release tablet, liquid
    d. Immediate-release tablet, extended-release tablet, orally disintegrating tablet

22. Which of the following is *false* with regard to tramadol?

- **a.** It is indicated for neuropathic pain.
- **b.** It can increase seizure risk with concurrent use of antidepressants.
- **c.** The dose should be reduced in cases of renal impairment.
- **d.** It is a controlled substance.

23. Which of the following narcotics is also commonly used as an antitussive?

- **a.** Tapentadol
- **b.** Codeine
- **c.** Morphine
- **d.** Hydrocodone

24. Which of the following brand name products contains hydrocodone and acetaminophen?

- **a.** Ultracet
- **b.** Percocet
- **c.** Norco
- **d.** Tylenol 3

25. Which of following will decrease the conversion of codeine to its active metabolite?

- **a.** CYP2D6 inducers
- **b.** CYP2D6 inhibitors
- **c.** CYP3A4 inducers
- **d.** CYP3A4 inhibitors

26. Ultrarapid metabolizers of codeine will have which of the following?

- **a.** No benefit from codeine
- **b.** Higher levels of morphine
- **c.** Lower levels of morphine
- **d.** Less analgesia from the codeine

27. Hydrocodone daily dosing is limited because of which of the following?

- **a.** It is a poor analgesic.
- **b.** It can cause seizures at higher doses.
- **c.** It has a acetaminophen or ibuprofen dosing limit.
- **d.** It has the potential for addiction.

28. The brand name drug Tylox contains which of the following?

- **a.** Oxycodone/ibuprofen
- **b.** Oxymorphone/acetaminophen
- **c.** Oxycodone/acetaminophen
- **d.** Hydrocodone/acetaminophen

29. Compared to naproxen, celecoxib has a lower incidence of which of the following adverse events?

- **a.** Renal toxicity
- **b.** Elevated blood pressure
- **c.** Peripheral edema
- **d.** Gastrointestinal ulcers

30. Which of following is an appropriate dose of celecoxib for osteoarthritis?

- **a.** 50 mg twice daily
- **b.** 100 mg twice daily
- **c.** 200 mg twice daily
- **d.** 400 mg twice daily