OPIOIDS

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OPIOID TREATMENT FOR PAIN

• Among the most universally effective analgesic agents
• Used routinely in the treatment of acute pain as well as cancer pain
• Long-term treatment of chronic nonmalignant pain remains controversial and can be associated with increased occurrence of depression and lower health-related quality of life
• Experts advocate individualizing therapy, developing appropriate and safe boundaries (opioid agreements and urine drug testing), and formulating a therapeutic treatment plan with goals.

NOMENCLATURE

• Opioid: all compounds that act via opioid receptors
• Opiate: compounds derived from poppy (Papaver somniferum)
• Narcotic: any of a class of substances that blunt the senses; should not be used to describe substances in a medical context.

RECEPTORS

• Specific receptors on cell membranes (i.e., μ, δ, κ)
• G-protein coupled
• Receptors in the spinal cord and the brain modulate analgesic effect.

SIDE EFFECTS AND ADVERSE REACTIONS (SEE ALSO CHAPTER 20)

• Respiratory depression: decreased respiratory rate, decreased responsiveness of brain stem to increased CO₂ levels in arterial blood
• Constipation: reduction in gastrointestinal motility
• Nausea and vomiting: activation of chemoreceptor trigger zone in the area postrema
• Pruritus: can be peripherally mediated secondary to histamine release (e.g., morphine) or centrally mediated
• Bradycardia: stimulation of vagal efferent output
• Pupillary constriction: activation of nucleus Edinger-Westphal accessory
• Tolerance
• Opioid-induced hyperalgesia
• Physical dependence
• Addiction

CLINICAL USAGE

• Immediate-acting opioid formulations are indicated for acute (e.g., postsurgical) pain.
• Extended-release opioid formulations are only used to treat chronic pain (malignant and nonmalignant).
• Opioid treatment in chronic nonmalignant pain states remains controversial.
• Tolerance occurs when the same dose administered repetitively leads to a decreased effect over time.
• Tolerance develops more rapidly to the euphoric effects of opioids and much less so to its gastrointestinal side effects
• Tolerance develops regardless of the mode of administration.
• An opioid rotation is performed when pain is not relieved by opioids that cause intolerable side effects.
• For an opioid rotation, lower doses than expected according to the equivalency conversion tables are used.
• Incomplete cross-tolerance, dissimilar receptor activities, and different metabolites are the basis for an opioid rotation to decrease side effects while improving analgesia.
• Opioid-induced hyperalgesia can occur following prolonged opioid administration and lead to increased pain.
### Route of Administration for Common Opioids

<table>
<thead>
<tr>
<th>Route</th>
<th>Indication</th>
<th>Commonly used agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Treatment of moderate or severe pain in patients who tolerate oral intake</td>
<td>Codeine, hydrocodone, morphine, oxycodone, hydromorphone, methadone, tramadol</td>
</tr>
<tr>
<td>IV</td>
<td>Treatment of moderate to severe pain or if unable to take medications by mouth</td>
<td>Morphine, fentanyl, hydromorphone, meperidine</td>
</tr>
<tr>
<td>IM</td>
<td>Alternative to IV administration. Associated with pain upon injection and unpredictable pharmacokinetic profile</td>
<td>Morphine, hydromorphone</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Treatment of moderate to severe pain in patients unable to tolerate oral medications. Alternative to long-acting oral preparations</td>
<td>Fentanyl patch</td>
</tr>
<tr>
<td>Rectal</td>
<td>Can be used as alternative route of administration of oral opioids especially in the palliative care setting</td>
<td>See oral agents</td>
</tr>
<tr>
<td>Transmucosal</td>
<td>Treatment of breakthrough pain. Analgesia within 5-10 minutes</td>
<td>Oral fentanyl &quot;lollipop&quot; and fentanyl effervescent buccal tablet</td>
</tr>
</tbody>
</table>

### Opioid Equivalency (also see Chapter 19)

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Type</th>
<th>Relative potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Oral</td>
<td>200</td>
</tr>
<tr>
<td>Codeine</td>
<td>Parenteral</td>
<td>130</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Oral</td>
<td>N/A</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Parenteral</td>
<td>0.1</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Oral</td>
<td>7.5</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Parenteral</td>
<td>1.5</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Oral</td>
<td>300</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Parenteral</td>
<td>75</td>
</tr>
<tr>
<td>Methadone</td>
<td>Oral</td>
<td>10</td>
</tr>
<tr>
<td>Methadone</td>
<td>Parenteral</td>
<td>5</td>
</tr>
<tr>
<td>Morphine</td>
<td>Oral</td>
<td>30</td>
</tr>
<tr>
<td>Morphine</td>
<td>Parenteral</td>
<td>10</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oral</td>
<td>20</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Parenteral</td>
<td>N/A</td>
</tr>
</tbody>
</table>

From The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins www.hopweb.org.
**Opioid Formulations Table**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Type</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Oral</td>
<td>15, 30, 60 mg or 15 mg/mL</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Transdermal</td>
<td>25, 50, 75, 100 µg/hr</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Transmucosal</td>
<td>200, 400, 600, 800, 1200,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1600 mg (Actiq)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Oral</td>
<td>1, 2, 4, 8 mg or 1 mg/mL</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Rectal suppository</td>
<td>3 mg</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>Oral</td>
<td>2 mg</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Oral</td>
<td>50, 100 mg or 10 mg/mL</td>
</tr>
<tr>
<td>Methadone</td>
<td>Oral</td>
<td>5, 10, 20 mg or 1, 2, 10 mg/mL</td>
</tr>
<tr>
<td>Morphine</td>
<td>Oral, immediate-release</td>
<td>10, 12, 30 mg, 2, 4, 20 mg/mL</td>
</tr>
<tr>
<td>Morphine</td>
<td>Oral, sustained-release</td>
<td>15, 33, 60, 100, 200 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oral, immediate-release</td>
<td>5, 10, 20, 20 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oral, sustained-release</td>
<td>5, 12, 39 mg, 1, 20 mg/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10, 20, 40, 80 mg</td>
</tr>
</tbody>
</table>

*The listed products are based on availability in the U.S. From: The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. www.hopweb.org.*

**Characteristic Properties of Commonly Used Opioids**

**Tramadol**
- Used for mild to moderate pain in doses of up to 400 mg/day
- Synthetic codeine analog that shares properties of both opioids and tricyclic antidepressants (TCA's); binds weakly to the μ opioid receptor
- Inhibits the reuptake of serotonin and norepinephrine, and promotes neuronal serotonin release
- Not currently listed as a controlled drug by the Drug Enforcement Agency (DEA)
- Adverse effects resemble those of opioids, in addition to potential for serotonin syndrome and elevated seizure risk with selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, or TCAs
- Available in immediate- and extended-release formulations

**Morphine**
- The most commonly used opioid for treating severe pain
- Wide availability, cost, effectiveness, and multiple formulations (e.g., oral, rectal, IV, intranasal, epidural, subcutaneous, intrathecal, and sustained-release)
- Metabolized in the liver, producing morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M3G is inactive; M6G is an active metabolite that exceeds morphine in potency and half-life.
- Both metabolites are excreted by the kidneys: patients with renal dysfunction may experience prolonged morphine effects.
- For decreased renal function, consider small doses of immediate-release morphine and/or reducing the dosing frequency.

**Codeine**
- Used for mild to moderate pain
- Available as a combination product with acetaminophen or aspirin
- Metabolized by liver: rate of demethylation (conversion) to morphine is highly variable based on genetic polymorphism, which can account for lack of analgesic properties in some individuals.
- Avoid using codeine in patients with renal failure because its active metabolites accumulate and can cause significant adverse effects.
- Metabolized to morphine and hydrocodone

**Hydromorphone**
- Used for severe pain
- Semi-synthetic derivative of morphine
- Shares equivalency with morphine in analgesic efficacy and adverse effects
**Properties and Dosing of Oral Opioid Preparations**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial dosage</th>
<th>Dosing interval</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; peak plasma concentration</th>
<th>Duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine sulfate controlled-release tablets (MS Contin&lt;sup&gt;4&lt;/sup&gt;)</td>
<td>15 mg</td>
<td>Q12 hr</td>
<td>2.5 hr</td>
<td>12 hr</td>
</tr>
<tr>
<td>Morphine sulfate extended-release capsules (Avinza&lt;sup&gt;5&lt;/sup&gt;)</td>
<td>30 mg</td>
<td>Q24 hr</td>
<td>9.5 hr</td>
<td>24 hr</td>
</tr>
<tr>
<td>Morphine sulfate extended-release capsules (Kadian&lt;sup&gt;6&lt;/sup&gt;)</td>
<td>20 mg</td>
<td>Q12-24 hr</td>
<td>8.6 hr</td>
<td>12-24 hr</td>
</tr>
<tr>
<td>Oxycodone controlled-release tablets (OxyContin&lt;sup&gt;7&lt;/sup&gt;)</td>
<td>16 mg</td>
<td>Q12 hr</td>
<td>2.7 hr</td>
<td>8-12 hr</td>
</tr>
<tr>
<td>Oxymorphone immediate-release tablets (Omnopir&lt;sup&gt;8&lt;/sup&gt;)</td>
<td>10 mg</td>
<td>Q6 hr</td>
<td>0.5 hr</td>
<td>4-6 hr</td>
</tr>
<tr>
<td>Oxymorphone extended-release tablets (Omnopin&lt;sup&gt;9&lt;/sup&gt;)</td>
<td>5 mg</td>
<td>Q12 hr</td>
<td>2-3 hr</td>
<td>12 hr</td>
</tr>
<tr>
<td>Oral transmucosal fentanyl citrate (Actiq&lt;sup&gt;10&lt;/sup&gt;)</td>
<td>200 mcg</td>
<td>Q 6 hr</td>
<td>20-40 min</td>
<td>3-4 hr</td>
</tr>
<tr>
<td>Transdermal fentanyl patch (Durogesic&lt;sup&gt;11&lt;/sup&gt;)</td>
<td>12.5 mg/h</td>
<td>Q 72 hr</td>
<td>27.5 hr</td>
<td>72 hr</td>
</tr>
<tr>
<td>Transmucosal (buccal) fentanyl (Fentora&lt;sup&gt;12&lt;/sup&gt;)</td>
<td>100 µg</td>
<td>Q 30 min</td>
<td>47 min</td>
<td>3-4 hr</td>
</tr>
</tbody>
</table>

**Opioid Antagonists**

**Naloxone**
- Opioid receptor antagonist used to treat opioid-induced toxicity, especially respiratory depression
- Small doses (e.g., 0.2 mg IV) to titrate to effect, rapidly reverse the effects of µ receptor agonists
- Can be administered IV, IM, SC
- Most rapid onset of action is ~2 minutes with IV administration.
- The duration of the antagonistic effect depends on the dose and often requires redosing and close monitoring following opioid agonist-induced toxicity.
- Mean half-life of 64 minutes

**Methylnaltrexone**
- Peripherally acting opioid receptor antagonist
- Used to treat opioid-induced constipation in patients receiving palliative care after failing laxative therapy
- Adult dosing: 12 mg SC subcutaneously
- Contraindicated in patients with suspected or confirmed bowel obstruction

**Combination Opioid Agonists/Antagonists**

Morphine/Naltrexone (Embeda<sup>13</sup>)
- Naltrexone is added to discourage abuse when crushed or snorted.
- Extended-release morphine pellets, each with an inner core of naltrexone hydrochloride
- Crushing or chewing the combination drug releases naltrexone and reverses morphine's subjective and analgesic effects
- There is no evidence that this technology decreases the likelihood for abuse.
Nonopioid Analgesic Medications

Approach to Pain Control

- Multimodal analgesia:
  - Minimizes dose requirements and potential toxicity associated with a single agent
  - Effective pain relief by additive or synergistic use of two or more analgesics
  - Reduces the amount of each agent will reduce incidence and severity of serious side effects
  - Employs variety of agents that interfere with pain transmission and perception in the central and peripheral nervous system
  - Examples: combinations of nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants (TCAs), anticonvulsants, opioids, neuromodulating medications, procedural interventions
  - Apply the World Health Organization (WHO) Cancer Pain laddering:
  - The WHO "three-step analgesic ladder" was developed in 1986.
  - Provides concrete tool for physicians worldwide to use in combating cancer pain with oral medications
  - Consider for use in non-cancer pain conditions as well

Figure 1, World Health Organization 3 Step analgesic ladder with examples of analgesics adapted from Management of cancer pain: Clinical practice guideline number 9, (AHCPR Pub No. 94-0592); Rockville, MD: US Dept of Health and Human Services, 1994.

- Begin with a nonopioid (e.g., acetaminophen, ibuprofen) and progress from weaker to stronger opioids (Step 1–Step 3) for incremental pain severity.
- Consider adjuvant medications (e.g., TCAs, antiepileptics) at any step of the ladder.
- Estimated that 70%-90% of cancer pain is relieved when clinicians apply the WHO ladder appropriately (J Pain Palliat Care Pharmacother 1995; 7(2):1076-1077).

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
- Used to treat mild to moderate acute and chronic pain, often due to musculoskeletal disorders
- Produce anti-inflammatory, analgesic, and antipyretic effects
- Use those with shorter half-life over the shortest period of time to minimize renal and gastrointestinal (GI) toxicity
- Pain associated with inflammatory conditions (rheumatoid arthritis, gout) is especially susceptible to NSAID therapy.
- NSAIDs are associated with significant renal, GI, and hematologic toxicity.
- NSAIDs can worsen preexisting kidney disease. Patients should be closely monitored with blood pressure and renal function tests within 2 week of starting therapy.
• NSAIDs work by inhibiting cyclo-oxygenase (COX) and thereby limiting prostaglandin production.
• Selective inhibition of COX-2 (Celecoxib) produces less GI toxicity and can increase cardiovascular disease risk.
• NSAIDs (except aspirin) are contraindicated in coronary artery bypass graft (CABG) surgery.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Nonsteroidal Anti-inflammatory Drugs</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin Ecton</td>
<td></td>
<td>Antiplatelet effects; inhibits COX-1 &amp; COX-2.</td>
</tr>
<tr>
<td>Celecoxib</td>
<td></td>
<td>Pain relief.</td>
</tr>
<tr>
<td>Diclofenac extended release Voltaren XR</td>
<td>25-50 mg PO Q4-6H (max 150 mg/d)</td>
<td>Topical formulation approved for osteoarthritis of joints.</td>
</tr>
<tr>
<td>Diclofenac gel 1%</td>
<td></td>
<td>Topical formulation approved for osteoarthritis of joints.</td>
</tr>
<tr>
<td>Ibuprofen Advil</td>
<td>200-400 mg PO Q4-6H (max 2,400 mg/d)</td>
<td>Half-life 2 hours.</td>
</tr>
<tr>
<td>Ketorolac Javelot</td>
<td>15-30 mg IV or IM (max 150 mg on first day, 120 mg day 2-5)</td>
<td>Parenteral formulation 60 not take &gt;3 days.</td>
</tr>
<tr>
<td>Mobic</td>
<td>7.5-15 mg PO Q24H</td>
<td>Half-life 14 hours.</td>
</tr>
<tr>
<td>Meclizine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>250-500 mg PO Q6-12H (max 1,500 mg/d)</td>
<td>Topical formulation approved for minor strains, sprains, and contusions.</td>
</tr>
<tr>
<td>Diclofenac patch 1.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Acetaminophen
• Para-aminophenol derivative used to treat mild to moderate pain
• Analogous and antipyretic activity similar to NSAIDs but weak anti-inflammatory effects
• No significant GI toxicity or platelet inhibition
• Combination products with opioids, although common, should be monitored to prevent acetaminophen-induced hepatotoxicity.
• Risk of acetaminophen hepatotoxicity at doses of higher than ~4 g/d in adults; lower doses can cause hepatotoxicity with concurrent alcohol intake or preexisting hepatic impairment.
• Can increase INR in patients taking warfarin; smaller doses are recommended for patients weighing 55 kg (maximum 2.6 g/d).
• Individuals who drink 66 g/d alcohol or those with a history of binge drinking should take no more than 2 g/d of acetaminophen.

Ketamine
• Potent analgesic effect mediated by N-methyl-D-aspartate (NMDA) receptor antagonism
• Used intravenously to treat severe acute pain
• Side effects include hypertension and alcohol withdrawal symptoms leading to tachycardia and hypertension.
• Higher doses are associated with psychogenic effects such as hallucinations, that can be attenuated by concomitant administration of benzodiazepines.
• Respiration is preserved.

Tricyclic Antidepressants (TCA)
• Psychopharmacology:
  • Mechanism of action is primarily mediated by the blockade of reuptake of norepinephrine and serotonin.
  • Sodium channel blockade
  • NMDA inhibition
  • Opioid receptor interaction
  • e-Adrenergic receptor blockade
  • TRPV1 receptor modulation.
Increased levels of norepinephrine and serotonin are thought to enhance activation of descending inhibitory neurons. Classification of antidepressants is typically by their specific neurotransmitter reuptake inhibition. These antidepressants that have a greater inhibition of norepinephrine reuptake are associated with better analgesic effect.

Relevant contraindications include cardiac arrhythmias, recent heart attack, epilepsy, narrow angle glaucoma, heart block, hyperthyroidism, urinary obstruction, and monoamine oxidase inhibitors.

Typical TCAs: amitriptyline, imipramine, nortriptyline, desipramine

Indications:
- TCAs are most effective in relieving neuropathic pain and central pain (Fig. 1).
- Diabetic peripheral neuropathic (DPN) and postherpetic neuralgia (PHN) pain
- Migraines, fibromyalgia

Side effects:
- Anticholinergic effects, orthostatic hypotension, cardiac conduction anomalies, weight gain, sedation, sexual dysfunction, restlessness

<table>
<thead>
<tr>
<th>Tricyclic Antidepressant Drugs for Treatment of Chronic Pain</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Start with 10-25 mg</td>
<td>Watch for worsening depression, risk for suicidal ideation</td>
</tr>
<tr>
<td>Imaprine</td>
<td>PO at bedtime</td>
<td></td>
</tr>
<tr>
<td>Tofranil</td>
<td>Twice by 10-25 mg every week to effective dose</td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>(max daily dose 150 mg/d)</td>
<td></td>
</tr>
<tr>
<td>Remeron</td>
<td>Desipramine</td>
<td></td>
</tr>
</tbody>
</table>

Anticonvulsants
- Most commonly used medication for neuropathic pain
- All have different mechanisms of action, although all thought to act as membrane stabilizers
- Indications: primarily used to treat neuralgias, peripheral neuropathy (e.g., alcohol, HIV, diabetes mellitus), posttraumatic neuralgia, painful diabetic neuropathy, postherpetic neuralgia, central pain conditions (e.g., post-stroke pain), and lumbar and cervical radiculopathy

Gabapentin (Neurontin)
- γ-Aminobutyric acid (GABA) analog that binds to a26 subunit of calcium channel and decreases neurotransmitter release, but exact mechanism is unknown.
- Typical dosage: 300 mg nightly, titrating by 300 mg every 3-5 days as tolerated to maximum dose of 1,200 mg t.i.d.
- Patients should receive up to 1,800 mg/d before treatment is considered a failure.
- Relatively good side-effect profile; lacks drug interactions.
- Very little metabolism of drug; renal excretion
- Often a first-choice anticonvulsant for treating chronic, neuropathic pain
- Common adverse effects: dizziness, somnolence, fatigue, and pedal edema

Indications:
- FDA approved for postherpetic neuralgia
- Painful diabetic neuropathy
- Central pain
- Phantom pain
- Malignant pain
- Trigeminal neuralgia
- HIV neuropathy
- Side effects:
  - Weight gain, somnolence, dizziness, nausea, depression, withdrawal (seizure) if abruptly discontinued

Carbamazepine (Tegretol)
- Related chemically and pharmacologically to the TCAs
- Inhibits norepinephrine reuptake and blocks sodium ionic conductance
- Moderately protein-bound
- Hepatic metabolism and renal excretion
- Typical dosage: 200 mg/d and titrating up by 200 mg every 1–3 days to a maximum dose of 1,300 mg/d
- Side effects:
  - Nausea, lethargy, somnolence, dizziness, GI irritation, astasia, vertigo
  - Thrombocytopenia, aplastic anemia, pancytopenia, and agranulocytosis can occur.
- Baseline CBC and liver function tests critical
- Indications:
  - FDA approved for trigeminal neuralgia (TN)
  - Painful diabetic neuropathy

Lamotrigine (Lamictal®)
- Phenyltriazine derivative
- Blocks sodium channels and inhibits glutamine release; may modulate potassium and calcium channels
- Metabolized by the liver
- Drug-drug interactions with carbamazepine, valproic acid, and phenobarbital
- Typical starting dose is 25 mg b.i.d. Slow weekly titration is important due to increased risk of rash. Increase by 25 mg per week until 100 mg b.i.d. Maximum dosage is 200 mg b.i.d.
- Side effects:
  - Rash (5%–10% risk), which can progress to Stevens-Johnson syndrome (0.3% risk); in adult: headache, somnolence, dizziness, astasia, GI disturbance, and blurred vision
  - Discontinue medication if rash develops
- Taper over a 2-week period
- Indications:
  - Painful diabetic neuropathy, HIV neuropathy, spinal cord injury pain, trigeminal neuralgia, central pain (e.g., post-stroke)

Pregabalin (Lyrica®)
- Acts at the α2δ subunit of calcium channels (five times the receptor affinity of gabapentin); exact mechanism unknown
- Increases GABA concentration
- Undergoes very little metabolism; renal excretion
- Typical dose: 75 mg PO, b.i.d. for 1 week, then increase to 150 mg PO b.i.d.
- Side effects:
  - Somnolence, dizziness, headache, nausea, weight gain
- Indications:
  - FDA approved for PHN, painful diabetic neuropathy, and fibromyalgia
  - Spinal cord injury pain

Tepoxatone (Topoma®)
- Blocks sodium and calcium channels, facilitates GABA-A receptors, and inhibits glutamate activity
- Undergoes very little metabolism; renal excretion
- Typical dose: 25 mg PO, then increase by 25 or 50 mg per week to maximum dose of 200 mg PO b.i.d.
- Side effects:
  - Renal stones (1.5% risk), dizziness, somnolence, visual changes, astasia, nervousness, weight loss, memory and concentration difficulty, paresthesia, possible taste perversion
- Indications:
  - Painful diabetic neuropathy

Oxcarbazepine (Trileptal®)
- Carbamazepine analog
- Binds to sodium channels, increases potassium flow, modifies calcium channels
- Extensively metabolized
- Typical dose: 150 mg PO b.i.d. and increase by 150 mg/d each week until maximum dose of 600–1,200 mg/d
- Common side effects: fatigue, dizziness, somnolence, astasia, nausea, visual changes
- Hypotension is possible, so serum sodium levels should be monitored
- Indications:
  - Preferred drug for treating TN due to favorable adverse-effect profile
  - Painful diabetic neuropathy

Muscle Relaxants
- Antispasmodics (muscle relaxants) are used to treat chronic pain conditions with associated muscle tension and spasms.
Baclofen (Lioresal®)
- Indications:
  - FDA approved for intrathecal use in spasticity (due to spinal cord injury, multiple sclerosis, or spinal cord lesions)
  - Neurogenic pain and TN
  - Mechanism of action is thought to be secondary to GABA-B agonist activity at the spinal level.
  - Anecdotal evidence that it has intrinsic analgesic properties
  - Typical starting dose is 5 mg PO t.i.d., and escalating by 5 mg every 3–4 days to a maximum dose of 80 mg/day.
  - Adverse effects: fatigue, sedation, orthostatic hypotension, hypoesthesia, ataxia, urinary frequency

Cyclobenzaprine (Flexeril®)
- Structurally similar to the TCAs
- Indications:
  - Peripheral muscle spams and painful musculoskeletal conditions
  - Mechanism of action probably related to its effect on polysynaptic reflexes and descending facilitator systems
  - Not effective for spasticity due to central nervous system (CNS) diseases
  - Typical dose is 5–10 mg PO t.i.d. with a maximum dose of 30 mg/day in divided doses
  - Adverse effects: sedation, xerostomia, dizziness, urinary retention, constipation:
    - Contraindicated with MAOIs, cardiac dysrhythmias, urinary obstruction, hyperthyroidism
  - Concurrent use with tramadol may increase seizure risk.

Tizanidine (Zanaflex®)
- Centrally acting α2 adrenergic agonist
- Decreases spasticity by increasing presynaptic inhibition of motor neurons and decreases sympathetic nervous system activity at the dorsal horn
- Structurally similar to clonidine
- Indications:
  - FDA approved for spasticity associated with spinal cord injury, multiple sclerosis
  - Symptomatically maintained pain and neuropathic pain (burning, electrical, lancinating), acute low back pain, myofascial pain
  - Possible intrinsic analgesic activity due to α2-adrenergic agonism
  - Adverse effects: sedation, dizziness, weakness, xerostomia
  - Typical dose is 2 mg nightly or t.i.d., increased to 8 mg Q6–8H.

Metaxalone (Skelaxin®) and Mebuxamic acid (Robaxin®)
- Centrally acting skeletal muscle relaxant
- Useful for muscle spasm and musculoskeletal pain
- Careful use in patients with severe hepatic or renal disease
- Mebuxamic acid contraindicated in epilepsy; long-term use of metaxalone requires monitoring of liver function tests.
- Adverse effects (metaxalone, mebuxamic acid): sedation
  - Typical dosing:
    - Metaxalone: 800 mg PO Q6–8H
    - Mebuxamic acid: 750 mg PO Q4H
- Metaxalone indications:
  - Acute musculoskeletal pain
- Mebuxamic acid indications:
  - Acute musculoskeletal pain

Carisoprodol (Soma®)
- Skeletal muscle relaxant
- Indications:
  - Mild analgesia for musculoskeletal pain
  - Enhances analgesic effects of other drugs
  - Active metabolite is meperidine, a sedative-hypnotic barbiturate.
  - Anxiolytic agent with properties similar to the benzodiazepines
  - Both carisoprodol and meperidine have abuse potential
  - Side effects: drowsiness and ataxia
  - Typical dose: 350 mg PO three to four times daily (max 2–3 weeks)

Topical Agents
Lidocaine Patch (Lidoderm®)
- Produces analgesia without causing local anesthesia
• Blocks sodium channels in small, sensitized pain fibers
• Useful for post-herpetic neuralgia (PHN), myofascial pain, and peripheral neuropathy
• Especially useful for allodynia
• Protects against mechanical irritation of sensitized skin
• Typical dose: lidocaine 5%, one to three patches at a time for 12 hours
• Side effects: rash, local anesthetic toxicity
• Indications:
  • FDA approved for use in PHN
  • Post-chorioamnionitis pain, CRPS, post-amputation pain, neuroma pain, DPN, meralgia paresthetica, post-mastectomy pain, intercostals neuritis, ilioinguinal neuritis

Cayenne Cream:
• Extract of hot chili peppers
• Depletes substance P and neuropeptides from nociceptive fibers, causing analgesia
• Indications:
  • Useful for PHN and osteoarthritis
• Side effects:
  • Burning, stinging sensation upon application
  • Local erythema
  • Not associated with systemic adverse effects
• Typical dose: 0.025% or 0.075% cream or lotion applied 3-5 times daily

Anxiolytics
• Psychopharmacology:
  • Depress CNS at the limbic system, cortex, and brainstem reticular activating system by facilitating GABA
• Indications:
  • Anxiety disorder associated with chronic pain
  • Muscle spasm
  • Sedation during procedural interventions
• Medications:
  • Clonazepam, lorazepam, midazolam, diazepam
• Side effects:
  • Sedation

Psychostimulants
• Psychopharmacology:
  • Stimulate the release of norepinephrine
  • As dose increases, dopamine and then serotonin released
• Indications:
  • Counter opioid-induced sedation
  • FDA approved for attention deficit disorder, Parkinson disease, narcolepsy
• Medications:
  • D-amphetamine, methylphenidate, modafinil (mechanism of action unclear)
• Side effects:
  • Hypertension, tachyarrhythmias, anxiety, anorexia, irritation

Antipsychotics
• Psychopharmacology:
  • Dopamine antagonism, and interactions at the cholinergic, α1-adrenergic, and histaminic systems
• Indications:
  • Migraine, may be useful in neuropathic pain
  • Counteract delirium, especially in cancer pain and postoperative pain
• Medications:
  • Chlorpromazine, prochlorperazine, haloperidol, methotrimeprazine, fluphenazine
• Side effects:
  • Extrapyramidal symptoms (acute dystonia, akathisia, pseudoparkinsonism, tardive dyskinesia)
  • Hormone alterations (amenorrhea, galactorrhea)
  • Hypothalamic dysfunction (SIADH)
  • Anticholinergic effects (xerostomia, blurred vision, constipation, urinary retention, confusion)
  • Histamine effects (sedation, cognitive dysfunction, weight gain)
  • α1-Adrenergic effects
  • Cardiovascular effects (hypotension, tachycardia, dizziness, fainting, electrocardiographic changes)
Implantable Devices: Spinal Cord Stimulation and Intrathecal Drug Delivery

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Spinal Cord Stimulation (SCS)

Mechanism of Action
- Gate-control theory: stimulation of large-diameter afferent inputs to the spinal cord leads to closing of the gate to transmission of pain-related information via Aβ and C fibers; modulation of neurotransmitters.
- Effects on spinal and supraspinal circuits: altered local neurochemistry at the dorsal horn and suppression of wide dynamic range interneurons.
- Restoration of oxygen supply/demand balance through altered sympathetic tone.

Indications for SCS
- Intractable radicular pain following spinal surgery, chronic regional pain syndrome (CRPS), neuropathic pain of the lower or upper extremities, phantom limb pain, chronic sciatic pain, intractable angina pectoris, peripheral vascular disease, visceral pain.

Contraindications for SCS
- Patient refusal or lack of informed consent.
- Localized or systemic infection.
- Coagulopathy.
- Elevated intracranial pressure.
- Gross spinal instability.
- Severe spinal stenosis (for percutaneously placed leads).
- Unresolved major psychiatric disorder.
- Surgical procedure within 6 months of a SCS trial.
- History of previous failure of SCS trial or system.
- Inability to control the device.
- Foreseeable need for magnetic resonance imaging in the future.
- Pregnancy.

Basic Technology
- Trial:
  - Initial placement of one or more temporary percutaneous SCS leads under fluoroscopic guidance.
  - Anatomic midline of the epidural space might not correlate with physiologic midline.
  - Proper lead placement is confirmed by asking patient to report level of paresthesias generated by the SCS.
  - Pulse generator is carried externally.
  - Duration of an average trial: 7 days.
  - Pre- and post-trial evaluation to include functional outcome, disability score, pain relief, areas of paresthesia, reduction of pain medication intake during trial.
  - Formal psychologic evaluation prior to permanent implantation is required.
- Permanent implantation:
  - Performed in the operating room under fluoroscopic guidance.
  - Percutaneous leads do not require laminotomy.
  - Paddle leads require laminotomy.
  - Lead is tunneled and connected to implantable pulse generator (IPG) device.

Complications/Limitations
- Inadvertent intrathecal puncture, postdural puncture headache.
- Epidural hematoma, paralytic CSF leak.
- Infectious complications, such as epidural abscess, meningitis.
- Lead migration.
- Breakage of lead isolation.
- Battery failure.
- Pain relief is often temporary (<1–2 years).

Outcomes
- Outcome data often based on nonrandomized trials with limited follow-up and lacking functional measurements.
- A decrease in pain (visual analog scale) has been described for CRPS, other neuropathic pain syndromes, radicular pain following back surgery, peripheral vascular disease, and intractable angina pectoris.
- SCS technology has also been used successfully in the treatment of peripheral neuralgia (e.g., occipital neuralgia).

**INTRATHecal DRUG DELIVERY SYSTEMS (IDDs)**

**Common Intrathecally Administered Analgesic Medications**
- Morphine is the only FDA-approved opioid for intrathecal use.
- Hydromorphone is not FDA-approved for intrathecal use.
- Bupivacaine is often used in combination with opioids, but is not FDA-approved for continuous intrathecal use or combination therapy.
- Ziconotide is an N-type voltage-sensitive Ca-channel blocker; high cost; approved for intrathecal use.
- Clonidine is an α2-agonist with analgesic efficacy; often used in combination with opioids or local anesthetics (not FDA approved for intrathecal use).

**Indications for Intrathecal Opioid Therapy**
- Chronic, intractable cancer pain
- Nonmalignant pain has been managed with intrathecal drug delivery systems; development of tolerance can become problematic.
- Ineffective systemic treatment or intolerable side effects from systemic agents
- Favorable response to a screening trial (e.g., >50% decline in pain)
- Life expectancy usually at least 3 months

**Basic Technology**
- **Trial:**
  - Intrathecal catheter is placed under fluoroscopic guidance and connected to external pump.
  - Inpatient stay is usually necessary to monitor for adverse events.
  - Duration of an average trial is 7 days.
  - Pre- and post-trial evaluation to include functional outcome, disability score, pain relief, medication side effects
- **Permanent Implantation:**
  - Performed in the operating room under fluoroscopy
  - Catheter is inserted into intrathecal space and advanced to lower thoracic spine.
  - Pump is usually implanted subcutaneously in the anterior abdominal wall, and catheter is tunneled across flank to the intrathecal space.
  - Pump is filled with medication and wound is closed.
  - Reservoir containing drug is refilled through a port accessed by a needle inserted through the skin.
  - Pump can be interrogated and controlled by an external device.

**Complications**
- Catheter malposition, catheter disconnection, infection
- Epidural or intrathecal hematoma
- Infection, including meningitis, epidural abscess, wound infection
- Cerebrospinal fluid leak
- Drug error/overdose
- Hardware malfunction
- Drug-related side effects, such as respiratory depression, nausea/vomiting, pruritus, urinary retention
- Abuse of device as conduit for illicit drugs

**Outcomes**
- In selected cancer pain patients, IDD's has been shown to result in improved analgesia and reduced side effects as compared to standard medical management.