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 CO_2 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 accessorius
- 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

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

Opioid Equivalency (also see Chapter 19)

Opioid	Type	Relative potency
Codeine	Oral	200
Codeine	Parenteral	130
Fentanyl	Oral	N/A
Fentanyl	Parenteral	0.1
Hydromorphone	Oral	7.5
Hydromorphone	Parenteral	1.5
Meperidine	Oral	300
Meperidine	Parenteral	75
Methadone	Oral	10
Methadone	Parenteral	5
Morphine	Oral	30
Morphine	Parenteral	10
Oxycodone	Oral	20
Oxycodone	Parenteral	N/A

From The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. www.hopweb.org.

Opioid Formulations Table

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

*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/d
- Synthetic codeine analog that shares properties of both opioids and tricyclic antidepressants (TCAs): 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 multiformulations (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
- Semisynthetic derivative of morphine
- Shares equivalency with morphine in analgesic efficacy and adverse effects

- Appears to have active, nonanalgesic metabolites that may cause neuroexcitatory effects (myoclonus, allodynia, seizures, confusion) at high doses or in the setting of renal failure

Fentanyl
- Used for severe pain
- Initially used as an intraoperative anesthetic, now also available as transdermal and transmucosal formulation
- Transdermal patch: alternative to oral opioids, especially when cancer or adverse treatment effects preclude the oral administration of analgesics.
- Fentanyl is 100 times more potent than morphine and is very lipid-soluble, leading to easy passage through the skin and mucous membranes.
- High cumulative doses lead to increasing context-sensitive half-life.

Oxycodone
- Often used in combination with acetaminophen, aspirin, and ibuprofen as a short-acting analgesic for moderate to severe pain
- Immediate- and controlled-release forms available
- The liver metabolizes oxycodone to small amounts of oxymorphone, the only active metabolite, and oxymorphone does accumulate in renal failure, along with the parent drug.
- Clinicians should prescribe oxycodone cautiously and carefully monitor symptoms of toxicity in patients with renal compromise.
- Combination drug with acetaminophen (Percocet®) is prevalent and has significant "street value."

Meperidine
- Used most often as an intraoperative analgesic.
- Small, single doses are effective for postoperative shivering.
- Local anesthetic properties.
- Avoid meperidine for the treatment of chronic pain and cancer pain due to its short duration of action and concerns over metabolic toxicity.
- Metabolized to normeperidine, which is eliminated by both the liver and the kidney; hepatic or renal dysfunction can lead to metabolite accumulation.
- Normeperidine toxicity manifests as shakiness, muscle twitches, myoclonus, dilated pupils, and seizures.

Methadone
- Long-acting μ and δ opioid receptor agonist.
- Causes monoamine reuptake inhibition, and has N-methyl-D-aspartate (NMDA) antagonist properties.
- Significant variability in plasma half-life between individuals
- Firmly binds to extravascular binding sites and releases slowly back into plasma, resulting in a characteristically long half-life.
- Plasma half-life is 24 hours; analgesic half-life is only 4–6 hours.
- Potential for delayed toxicity (e.g., respiratory depression) from drug accumulation in tissues; repeat administration coupled with a prolonged half-life increase the risk of overdose.
- Possible QT prolongation and torsades de pointes if taking >300 mg/d, or with concurrent use of antidepressants, or in conditions with hypokalemia or hypomagnesemia, and congestive heart failure.
- Inexpensive

Buprenorphine
- Partial agonist at the μ opioid receptor and an antagonist at the κ and δ receptors.
- High affinity for and slow dissociation from the μ receptor, and may produce less analgesia than a full μ agonist.
- Available in combination with naloxone to prevent diversion for IV use.
- Patients on buprenorphine might require transition to a pure opioid agonist prior to elective surgery.
- In patients presenting for unscheduled surgery, high doses of a pure opioid agonist such as fentanyl might be required.

Oxymorphone
- Metabolite of oxycodone
- Indicated for moderate to severe pain
- Available in immediate- and extended-release oral formulations
- Analgesia mediated through μ and δ opioid receptors
- Long half-life of immediate release formulation (7–9 hours)
- Renal excretion

Properties and Dosing of Oral Opioid Preparations

Medication	Initial dosage	Dosing interval	T_{max} peak plasma concentration	Duration of action
Morphine sulfate controlled–release tablets (*MS Contin®*)	15 mg	Q12 hr	2.5 hr	12 hr
Morphine sulfate extended–release capsules (*Avinza®*)	30 mg	Q24 hr	9.5 hr	24 hr
Morphine sulfate extended–release capsules (*Kadian®*)	20 mg	Q12–24 hr	8.6 hr	12–24 hr
Oxycodone controlled–release tablets (*OxyContin®*)	10 mg	Q12 hr	2.7 hr	8–12 hr
Oxymorphone immediate–release tablets (*Opana IR®*)	10 mg	Q6 hr	0.5 hr	4–6 hr
Oxymorphone extended–release tablets (*Opana ER®*)	5 mg	Q12 hr	2–3 hr	12 hr
Oral transmucosal fentanyl citrate (*Actiq®*)	200 mcg	Q 6 hr	20–40 min	3–4 hr
Transdermal fentanyl patch (*Duragesic®*)	12.5 mcg/h	Q 72 hr	27.5 hr	72 hr
Transmucosal (buccal) fentanyl (*Fentora®*)	100 μg	Q 30 min X1, then Q4 hr	47 min	3–4 hr

Opioid Antagonists

Naloxone

- Opioid receptor antagonist used to treat opioid-induced toxicity, especially respiratory depression
- Small doses (e.g., 0.2 mg IV)m titrated 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/d subcutaneously
- Contraindicated in patients with suspected or confirmed bowl obstruction

Combination Opioid Agonists/Antagonists

Morphine/Naltrexone (Embeda®)

- 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

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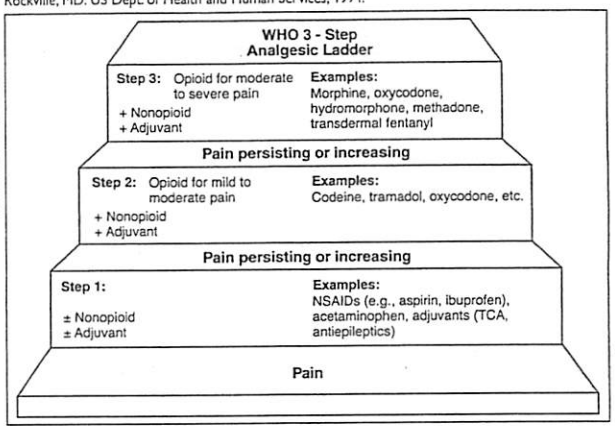
Approach to Pain Control

- 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
  - Reducing 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, neuraxial medications, procedural interventions
  - Apply the *World Health Organization (WHO) Cancer Pain "Ladder"*:
    - 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 (Jadad, AR & Browman GP. JAMA 1995; 274:1870–1873).

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.

Nonsteroidal Anti-inflammatory Drugs

Drug	Dose	Comments
Aspirin *Ecotrin*®	500-1,000 mg PO Q 4–6H (max 4,000 mg/d)	Inactivation of COX via acetylation Potent inhibitor of platelet aggregation Do not use in children (risk of Reye syndrome)
Celecoxib *Celebrex*®	100–200 mg PO b.i.d.	Not to be taken if allergic to sulfa Minimizes GI toxicity
Diclofenac extended release *Voltaren XR*®	25–50 mg PO Q4–6H (max 150 mg/d)	
Diclofenac gel 1%	Apply 2–4 g topically (max 32 g/d)	Topical formulation approved for osteoarthritis of joints
Ibuprofen *Advil*®	200–400 mg PO Q4–6H (max 2,400 mg/d)	Half-life 2 hours
Ketorolac *Toradol*®	15–30 mg IV or IM (max 150 mg on first day, 120 mg day 2–5)	Parenteral formulation do not take >5 days
Meloxicam *Mobic*®	7.5–15 mg PO Q24H	
Naproxen *Naprosyn*®	250–500 mg PO Q8–12H (max 1,500 mg/d)	Half-life 14 hours
Diclofenac patch 1.3%	Apply 1 patch b.i.d.	Topical formulation approved for minor strains, sprains, and contusions

Acetaminophen

- Para-aminophenol derivative used to treat mild to moderate pain
- Analgesic 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 concomitant alcohol intake or preexisting hepatic impairment.
- Can increase INR in patients taking warfarin; smaller doses are recommended for patients weighing 50 kg (maximum 2.6 g/d).
- Individuals who drink 60 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 hypersalivation and indirect sympathomimetic properties 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
  - α-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.
- Those 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
    - Migraine, fibromyalgia
- Side effects:
  - Anticholinergic effects, orthostatic hypotension, cardiac conduction anomalies, weight gain, sedation, sexual dysfunction, restlessness

Tricyclic Antidepressant Drugs for Treatment of Chronic Pain

Drugs	Dose	Comments
Amitriptyline *Elavil*® Imipramine *Tofranil*® Nortriptyline *Pamelor*® Desipramine *Norpramin*®	Start with 10–25 mg PO at bedtime Titrate by 10–25 mg every week to effective dose (max daily dose 150 mg/d)	Watch for worsening depression, risk for suicidal ideation Contraindications: cardiac arrhythmias, recent myocardial infarction (MI), epilepsy, narrow angle glaucoma, heart block, hyperthyroidism, monoamine oxidase inhibitor (MAOI) therapy, urinary retention, alcohol abuse

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 α2δ subunit of calcium channel and decreases neurotransmitter release, but exact mechanism is unknown.
- Typical dosage: 300 mg nightly, and titrating by 300 mg every 3–5 days as tolerated to maximum dose of 1,200 mg t.i.d.
- Patient 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 1,500 mg/d
- Side effects:
  - Nausea, lethargy, somnolence, dizziness, GI irritation, ataxia, 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 staring 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 250 mg b.i.d.
- Side effects:
  - Rash (9%–10% risk), which can progress to Stevens-Johnson syndrome (0.3% risk in adults); headache, somnolence, dizziness, ataxia, 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 $\alpha 2\delta$ 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

Topiramate (Topamax®)
- Blocks sodium and calcium channels, facilitates GABA-A receptors, and inhibits glutamate activity
- Undergoes very little metabolism; renal excretion
- Typical dose: 25 mg/d 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, ataxia, nervousness, weight loss, memory and concentration difficulty, paresthesias, possible taste perversions
- 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, ataxia, nausea, visual changes:
  - Hyponatremia 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)
  - Neuropathic 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 staring dose is 5 mg PO t.i.d., and escalating by 5 mg every 3–4 days to a maximum dose of 80 mg/d.
- Adverse effects: fatigue, sedation, orthostatic hypotension, hypotonia, ataxia, urinary frequency

Cyclobenzaprine (Flexeril®)
- Structurally similar to the TCAs
- Indications:
  - Peripheral muscle spasms 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) disease
- Typical dose is 5–10 mg PO t.i.d. with a maximum dose of 30 mg/d 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
  - Sympathetically maintained pain and neuropathic pain (burning, electrical, lancinating), acute low back pain, myofascial pain
- Possible intrinsic analgesic activity due to α-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 Methocarbamol (Robaxin®)
- Centrally acting skeletal muscle relaxants
- Useful for muscle spasms and musculoskeletal pain
- Careful use in patients with severe hepatic or renal disease
- Methocarbamol contraindicated in epilepsy; long-term use of metaxalone requires monitoring of liver function tests.
- Adverse effects (metaxalone, methocarbamol): sedation
- Typical dosing:
  - Metaxalone: 800 mg PO Q6–8H
  - Methocarbamol: 750 mg PO Q4H
- Metaxalone indications:
  - Acute musculoskeletal pain
- Methocarbamol indications:
  - Acute musculoskeletal pain

Carisoprodol (Soma®)
- Skeletal muscle relaxant
- Indications:
  - Mild analgesia for musculoskeletal pain
- Enhances analgesic effects of other drugs
- Active metabolite is meprobamate, a sedative-hypnotic barbiturate.
- Anxiolytic agent with properties similar to the benzodiazepines
- Both carisoprodol and meprobamate 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: lidoderm 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-thoracotomy pain, CRPS, post-amputation pain, neuroma pain, DPN, meralgia paresthetica, post-mastectomy pain, intercostals neuralgia, ilioinguinal neuralgia

Capsaicin 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:
  - Dextroamphetamine, 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 Aδ 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 paresthesias, 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, paralysis, 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 $\alpha 2$-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: 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

- Pump malposition, catheter disconnect/kink
- Epidural or intrathecal hematoma
- Infectious complications, such as meningitis, epidural abscess, wound infection
- Cerebrospinal fluid leak
- Drug error/overdose
- Hardware malfunction
- Drug-related side effects, such as respiratory depression, nausea/emesis, pruritus, urinary retention
- Abuse of device as conduit for illicit drugs

Outcomes

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