Pain Management: Beyond the Basics

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May 2025

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Objectives

- Discuss the various medication options for long-acting pain control, including costs, metabolic considerations, dose forms, and dosing considerations
- Review appropriate use and dosing of short-acting pain medications
- Provide strategies for using opioids for dyspnea and neuropathic pain
- Recognize opioid toxicity and review management strategies
- Understand the use of methadone, buprenorphine, and ketamine
- Understand options for alternative (non-oral) routes of administration of opioids

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Knowledge Check

When **starting** opioids on a hospice patient, which of the following needs to be considered when choosing an appropriate **dose**:

a. The severity of the pain
b. Whether the patient can take long-acting pain medicines
c. Age/organ dysfunction
d. All of the above

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Opioid Naïve Dosing

- Taking less than 60 mg OME/day for less than a week
- Unintentional overdose may be more likely if opioid therapy is initiated with long-acting opioids (FIVE TIMES MORE LIKELY)
- **Start low and go slow**
- Dose and frequency adjustment may be necessary for the elderly or those with organ dysfunction

ORAL OPIOID FORMULATION	SUGGESTED INITIAL DOSING FOR OPIOID-NAÏVE PATIENT
Morphine Immediate-Release	5mg by mouth every 4 hours as needed
Oxycodone Immediate-Release	5mg by mouth every 4 hours as needed
Oxymorphone Immediate-Release	5mg by mouth every 4 hours as needed
Hydromorphone Immediate-Release	2mg by mouth every 4 hours as needed

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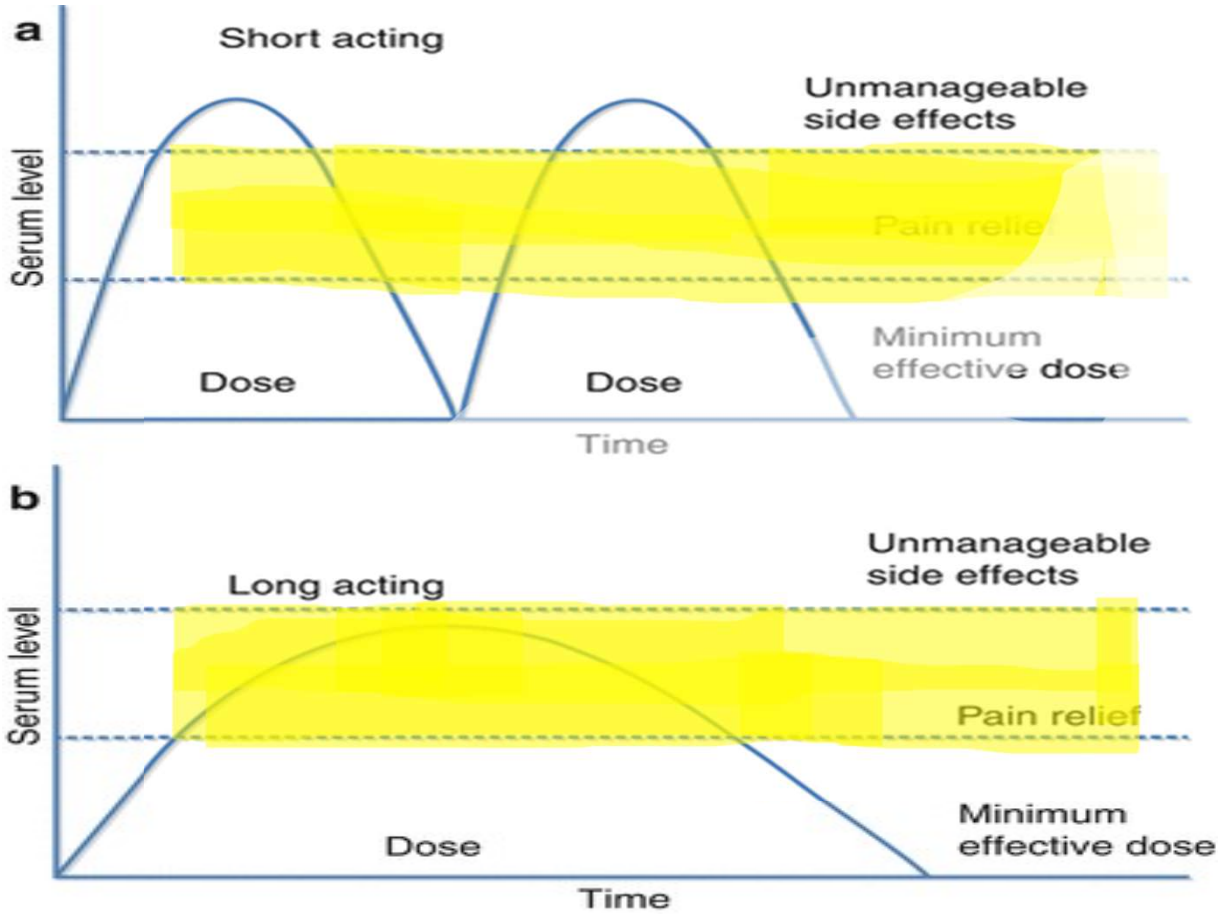
Short-Acting vs. Long-Acting Opioids



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Short-Acting Vs. Long-Acting Opioids

- Always provide a short-acting (breakthrough) pain medication along with a long-acting formulation
- Patients frequently requiring PRN pain medication may benefit from an increase in long-acting pain medication
- Don’t forget the PRN should be 10-20% of the total oral dose…increase this when increasing the long-acting!

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Knowledge Check

Patients who have renal or hepatic impairment may have:

a. Increased likelihood of adverse events/toxicity without dose adjustment

b. Potential for decreased analgesic effect

c. Potential for increased half-life/duration of action

d. All of the above

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Dosing With Renal/Hepatic Impairment

- Renal impairment affects the clearance of many opioids
- Hepatic impairment affects the metabolism of many opioids
- Increased likelihood of adverse events/toxicity without dose adjustment
- Potential for decreased analgesic effect
- Potential for increased half-life/duration of action
- Can precipitate or aggravate hepatic encephalopathy in patients with severe liver disease

Owsiany MT, Hawley CE, Triantafylidis LK, Paik JM. Opioid Management in Older Adults with Chronic Kidney Disease: A Review. Am J Med. 2019 Dec;132(12):1386-1393. doi: 10.1016/j.amjmed.2019.06.014. Epub 2019 Jul 8. PMID: 31295441; PMCID: PMC6917891.
Soleimanpour H, Safari S, Shahsavari Nia K, Sanaie S, Alavian SM. Opioid Drugs in Patients With Liver Disease: A Systematic Review. Hepat Mon. 2016 Mar 6;16(4):e32636. doi: 10.5812/hepatmon.32636. PMID: 27257423; PMCID: PMC4887963

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Opioids in Renal Impairment

Table 4. Dosage Adjustment Based on GFR

GFR (mL/min)	Morphine	Hydromorphone	Oxycodone	Methadone	Fentanyl
>50	100% of original dosing	50%-100% of original dosing	100% of original dosing	100% of original dosing	100% of original dosing
10-50	50%-75% of original dosing	50% of original dosing	50% of original dosing	100% of original dosing	75%-100% of original dosing
<10	Not recommended	25% of original dosing	Not recommended	50%-75% of original dosing	50% of original dosing

GFR: glomerular filtration rate. Source: Reference 16.

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Opioids in Hepatic Impairment

Table 3. Recommendations for Opioids in Hepatic Impairment

Opioid	Recommendations
Codeine	Not recommended; in severe hepatic dysfunction codeine is not converted to morphine, leading to poor analgesia
Fentanyl	99% metabolized in liver; studies have not demonstrated PK alterations; careful monitoring is warranted
Hydrocodone	Use with caution; monitor for overdose due to parent compound not being converted to metabolites
Hydromorphone	Undergoes phase II reaction; however, use with caution due to its intermediate extraction ratio
Methadone	Use with caution; risk of accumulation because of increased free drug
Meperidine	Not recommended; toxic metabolite, normeperidine, may accumulate
Morphine	Use with caution; monitor for overdose due to high extraction ratio
Oxycodone	Use with caution; dose adjustment recommended (1/2 to 1/3 of original dose)
Oxymorphone	Contraindicated in moderate-to-severe hepatic impairment
Tramadol	Not recommended; significant PK changes in moderate-to-severe hepatic impairment

PK: pharmacokinetics. Source: References 8, 16.

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Knowledge Check

Which of the following are options for pain for patients unable to swallow whole opioids in tablet form?

a. Crushing immediate release tablets or using an oral liquid
b. Subcutaneous administration of morphine, hydromorphone
c. Rectal administration
d. Topical gels
e. A,B,C only

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Non-Oral Dosage Forms

Route	Advantages	Cautions/Notes	Medications
Transdermal Patches	• Ease of administration • Extended duration of action (3-7 days) • Good patient compliance • Painless • As compared with oral morphine, transdermal fentanyl and buprenorphine have been shown to produce less constipation, nausea/vomiting, and vertigo/somnolence	• Local irritation can occur at patch site • Contraindicated in patients with acute or uncontrolled pain • Should only be used in patients with stable pain because of the longer titration interval • Increased skin temperature increases absorption; (fever, heating blankets (3x!) • Patch must adhere properly to skin to ensure absorption	Fentanyl Buprenorphine
Sublingual/ Buccal	• Rapid onset of action for highly lipophilic drugs (e.g., fentanyl and methadone)	• Hydrophilic drugs such as morphine and hydrocodone are poorly absorbed sublingually • Bitter taste and burning sensation possible • Need to retain the drug sublingually for several minutes • Studies have not provided compelling evidence for the effectiveness of SL morphine for rapid pain relief	• All oral drugs (see notes re: absorption) • Fentanyl buccal tablet • Buprenorphine buccal film, SL tab

Matthew G. Kestenbaum, Agustin O. Vilches, Stephanie Messersmith, Stephen R. Connor, Perry G. Fine, Brian Murphy, Malene Davis, J. Cameron Muir, Alternative Routes to Oral Opioid Administration in Palliative Care: A Review and Clinical Summary, *Pain Medicine*, Volume 15, Issue 7, July 2014, Pages 1129–1153, https://doi.org/10.1111/pme.12464

Subcutaneous(SQ) Opioids

Opioids can be given SQ without access to a vein, at the same dose as IV, to achieve similar blood levels as IV

- Morphine, hydromorphone, fentanyl can all be safely administered as SQ bolus doses or continuous SQ infusion
- Methadone SQ infusions have been associated with more frequent local skin irritation; improved with frequent site rotation

PCNOW Fast Fact #28 Subcutaneous Opioid https://www.mypcnow.org/fast-fact/subcutaneous-opioid-infusions/

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Subcutaneous(SQ) Opioids

- SQ bolus injections onset of action around 5 minutes (faster for fentanyl)
- No data to suggest that cachectic, febrile, or hypotensive patients have problems with drug absorption
- Subcutaneous tissue can absorb up to 3 ml/hr
  - At low opioid requirements morphine is generally the drug of choice
  - Switch to hydromorphone for a high opioid requirement since it's more potent (smaller infusion volume)

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Giving Medications Per Rectum

- Any pill can be given rectally; the suppository form merely assists in its retention
- Extent of absorption and timing of effect can vary greatly
- Retention is superior when the base (blunt end) is inserted first
- Drugs administered through the rectum, especially opioids, are dosed similarly as when given orally (possible exception for seizure meds)
- 10 ml warm water can be inserted via syringe to assist dissolution of the suppository or suspension
- Keep volume of drug preparation less than 60 ml to avoid spontaneous expulsion before absorption

Opioids	Steroids	NSAIDs/APAP	Anxiolytics	Antipsychotics	Anti-Emetics	Seizure Meds
Morphine Hydromorphone Methadone Oxycodone Codeine Tramadol	Dexamethasone	APAP Diclofenac Indomethacin Ibuprofen Naproxen Aspirin	Lorazepam Midazolam Clonazepam	Olanzapine Haloperidol Chlorpromazine	Ondansetron Metoclopramide	Phenobarbital Levetiracetam Lamotrigine Valproic Acid Carbamazepine

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PC NOW Fast Fact #257 Palliative Care Per Rectum available at https://www.mypcnow.org/fast-fact/palliative-care-per-rectum/

Knowledge Check

TRUE or FALSE

For patients with persistent dyspnea, it's best to limit opioid use to PRN, and only for severe dyspnea

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Opioids for Dyspnea

- Opioids appear to modulate anticipatory breathlessness and the sensation of breathlessness; reduce the “urge to breathe”
- Response is reduced by anxiety, depression (so treat these, also)
- Most of the evidence is in people with COPD; not all disease states have breathlessness that responds to morphine
- **Most effective in steady state as opposed to single dose (in studies)**
- Guidelines for management of dyspnea from several expert groups, (ASCO, ACCP, ATS, NCCN) all advise the use of systemic opioids for relief of dyspnea in patients with advanced terminal disease with appropriate caution regarding the risk of respiratory depression

Opioid Naïve	Currently on Opioid
Moderate dyspnea: oral morphine 5 mg q 4-5 h regularly and 2.5 mg q 2 h PRN; convert to long-acting when effective regular dose is determined; can use3 mg SQ 4 h regularly and 1.5 qh PRN	Increase daily dose: Increase regular total daily dose by 25%
Severe dyspnea: morphine 2.5 mg SQ every 30-60 min; if two doses are well tolerated but fail to reduce dyspnea, double the dose	Breakthrough dose: 10% of regular total oral daily dose q 2h PRN; 5% of daily oral dose SQ q hour

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Knowledge Check

If a patient complains of burning/stabbing/shooting pain, the best option may be to:

a. Start an opioid or increase the dose of existing opioid
b. Change to a different opioid
c. Add a medication such as duloxetine or gabapentin
d. Add an NSAID such as ibuprofen or meloxicam
e. All of the above

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Opioids for Neuropathic Pain

2013 Cochrane review and a follow-up review in 2019

- Found limited evidence for buprenorphine, morphine, oxycodone, tramadol, and tapentadol in postherpetic neuralgia and peripheral neuropathy
- Limited evidence for methadone

Burning
Tingling
Stabbing
Shooting
Electric Shock
Numbness
Pins and Needles

Methadone in Pain Management: A Systematic Review. Hanna V, Senderovich H. Journal of Pain Vol 22, Issue 3. 2021 233-245
Kreutzwiser D, Tawfic QA. Methadone for Pain Management: A Pharmacotherapeutic Review. *CNS Drugs*. 2020;34(8):827-839. doi:10.1007/s40263-020-00743-3

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Non-Opioid Medications for Neuropathic Pain

2023 Cochrane Review of antidepressants for neuropathic pain

- "The only antidepressant we are certain about for the treatment of chronic pain is duloxetine
- Duloxetine was moderately efficacious across all outcomes at standard dose
- Evidence for all other antidepressants was low certainty"

2022 Cochrane Review of topical clonidine

- "Topical clonidine (TC) may provide some benefit to adults with painful diabetic neuropathy; however, the evidence is very uncertain."

Birkinshaw H, et al. Antidepressants for pain management in adults with chronic pain: a network meta-analysis. Cochrane Database of Systematic Reviews 2023, Issue 5. Art. No.: CD014682.
Serednicki WT, et al. Topical clonidine for neuropathic pain in adults. Cochrane Database of Systematic Reviews 2022, Issue 5. Art. No.: CD010967.

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Non-Opioid Medications for Neuropathic Pain

2017 Cochrane Review of gabapentin for neuropathic pain

- "Gabapentin at doses of 1800 mg to 3600 mg daily can provide good levels of pain relief to some people with postherpetic neuralgia and peripheral diabetic neuropathy. Evidence for other types of neuropathic pain is very limited.
- Over half of those treated with gabapentin will not have worthwhile pain relief but may experience adverse events."

2019 Cochrane Review of pregabalin for neuropathic pain

- "Evidence shows efficacy of pregabalin in postherpetic neuralgia, painful diabetic neuralgia, and mixed or unclassified post-traumatic neuropathic pain, and absence of efficacy in HIV neuropathy
- Evidence of efficacy in central neuropathic pain is inadequate.
- Some people will derive substantial benefit with pregabalin; more will have moderate benefit, but many will have no benefit or will discontinue treatment."

2017 Cochrane Review of oxcarbazepine for neuropathic pain

- "Little evidence to support the effectiveness of oxcarbazepine in painful diabetic neuropathy, neuropathic pain from radiculopathy and a mixture of neuropathies"

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Wiffen PJ, et al. Gabapentin for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews 2017, Issue 6. Art. No.: CD007938.
Zhou M, et al. Oxcarbazepine for neuropathic pain. Cochrane Database of Systematic Reviews 2017, Issue 12. Art. No.: CD007963.
Derry S, et al. Pregabalin for neuropathic pain in adults. Cochrane Database of Systematic Reviews 2019, Issue 1. Art. No.: CD007076

Other Treatments for Neuropathic Pain

2022 Cochrane Review of cannabinoids

"We found only one small trial that measured the number of participants reporting substantial pain relief with a synthetic cannabinoid compared with placebo (OR 4.23, 95% CI 1.11 to 16.17; 1 study, 48 participants; very low-certainty evidence). We are uncertain whether cannabinoids reduce chronic neuropathic pain intensity."

2019 Cochrane Review of herbal medicinal products for neuropathic pain

"There was insufficient evidence to determine whether nutmeg or St John's wort has any meaningful efficacy in neuropathic pain conditions."

Filippini G, et al. Cannabis and cannabinoids for symptomatic treatment for people with multiple sclerosis. Cochrane Database of Systematic Reviews 2022, Issue 5. Art. No.: CD013444.
Boyd A, et al. Herbal medicinal products or preparations for neuropathic pain. Cochrane Database of Systematic Reviews 2019, Issue 4. Art. No.: CD010528.

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Knowledge Check

Signs of opioid neurotoxicity include:

a. Mental status changes
b. Seizures/myoclonus
c. Allodynia and/or hyperalgesia (“disordered” pain)
d. All of the above

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Opioid-Induced Neurotoxicity (OIN)

Symptoms

- Severe sedation
- Delirium
- Hallucinations
- Myoclonus
- Seizures
- Hyperalgesia
- Allodynia

Contributory factors

- Large doses of opioids
- Chronic use of opioids
- Rapid dose escalation
- Older age
- Renal failure
- Infection
- Dehydration

Opioids with Active Metabolites

- Codeine
- Hydrocodone
- Hydromorphone
- Meperidine
- Morphine
- Oxycodone

Godwin B et al. Identification and management of opioid-induced neurotoxicity in older adults. Can Fam Physician. 2022 Apr;68(4):269-270.

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Drug-Drug Interactions with Opioids

- Codeine, hydrocodone, oxycodone, methadone, tramadol, fentanyl undergo Phase 1 metabolism by CYP3A4 and/or 2D6
- Calcium channel blockers, statins, amiodarone, SSRIs, anti-HIV agents, macrolide antibiotics, steroids, beta blockers may interact
- Hydromorphone, oxymorphone, morphine do not have phase 1 metabolism

Gudin, Jeffrey. "Opioid therapies and cytochrome p450 interactions." *Journal of pain and symptom management* 44.6 (2012): S4-S14.

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CS0

Opioid Neurotoxicity vs Overdosing

- Mental Status Changes
- Cardiovascular Status
- Respiratory Status
- Hypoactive Bowel Sounds
- Miosis

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Slide 27

CS0 are these images? consider typing out the Diagnosis box in particular because everything is to the top of the image compared to the toxicity/overdosing box, which everything is centered. And it will probably be easier to read

Cheng, Stephanie, 2025-03-27T15:00:17.679

Diagnosis of Opioid Neurotoxicity

Two or More

- At least two opioid dose escalations
- No improvement in pain or worsened pain
- Volume depletion or renal insufficiency

Plus One or More

- Hyperalgesia
- Hyperesthesia
- Allodynia
- Myoclonus/Seizures
- Delirium

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Opioid Neurotoxicity Management

- Hydration
- Dose reduction: 25% reduction should not result in withdrawal symptoms
- Opioid Rotation
  - Begin the new opioid at 50% of the equivalent of the offending medication (25% if on very high dose)
  - Methadone and fentanyl may be good choices as they have no active metabolites
- Adjunctive medications
  - Add medication therapy to treat symptoms of OIN and/or reduce the patient's opioid requirements
  - Myoclonus- consider medications such lorazepam, clonazepam, cyclobenzaprine; hallucinations/delirium consider haloperidol
  - Nonopioid analgesics, such as NSAIDs (e.g., ibuprofen) may help to decrease opioid dose and frequency needs

Kozlov M, Anderson MA, and Sparbel K. Opioid-Induced Neurotoxicity in the Hospice Patient. Journal of Hospice & Palliative Nursing. 2011; 13(5): 334-339.

Gallagher R. Opioid-induced neurotoxicity. Canadian Family Physician. 2007;53: 426-427.

Wilson RK et al. Fast Fact #58 Neuroexcitatory Effects of Opioids: Treatment Palliative Care Network of Wisconsin, available at FF #58 Neuroexcitatory Effects of Opioids: Treatment | Palliative Care Network of Wisconsin

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Opioid Adjuvants

NON-OPIOIDS					
CLASSIFICATION	**MEDICATIONS**		**PLACE IN THERAPY**	**CONSIDERATIONS**	**ADVERSE EFFECTS**
PARA-AMINOPHENOL DERIVATIVES	Acetaminophen		Mild somatic pain; fever	Ceiling effect; favorable side effect profile; max dose of 3g/day	hepatotoxicity; hypothermia; rash
NSAIDS	Aspirin Diclofenac Ibuprofen	Nabumetone Naproxen	Mild to moderate inflammatory pain; bone pain; fever	Dose-dependent effects; enhance opioid analgesia; selection based on toxicities, experience, convenience	Platelet dysfunction; GI toxicity; confusion; renal toxicity; fluid retention; salicylism
ADJUVANTS					
CORTICOSTEROID	Dexamethasone Methyl-prednisolone	Prednisone Prednisolone	Reduce swelling/ inflammation; visceral distention; feeling of well-being; bone pain	Mood elevation; anti-emetic; appetite stimulation; weight gain	Insomnia; nervousness; increased appetite & indigestion; hyperglycemia; immunosuppression
ANTIDEPRESSANT	Amitriptyline Desipramine Doxepin	Nortriptyline Venlafaxine	Neuropathic pain; depression; insomnia	Lower doses & faster onset of pain relief compared use for depression; drug-drug interactions	TCAs: anticholinergic side effects Venlafaxine: dose-dependent hypertension
ANTICONVULSANT	Carbamazepine Gabapentin Valproic Acid		Neuropathic pain; seizures; stabilize mood	Multiple mechanisms of action; may require serum monitoring; drug-drug interactions	Carbamazepine: blood dyscrasias Gabapentin: drowsiness Valproic acid: hepatoxicity; pancreatitis
ANTISPASMODIC	Dicyclomine Hyoscyamine Glycopyrrolate		Abdominal cramping/ pressure; sialorrhea	Potential to alleviate pain from bowel obstruction by reducing motility	Anticholinergic side effects
OTHER	Ketamine		Neuropathic pain; hyperalgesia; allodynia	Compounded product	Mental clouding; mood changes

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Knowledge Check

The idea methadone candidate

a. Has a short prognosis

b. Has moderate to severe pain

c. Would benefit from a long-acting pain medication but is unable to swallow whole tablets

d. ALL OF THE ABOVE

e. B and C only

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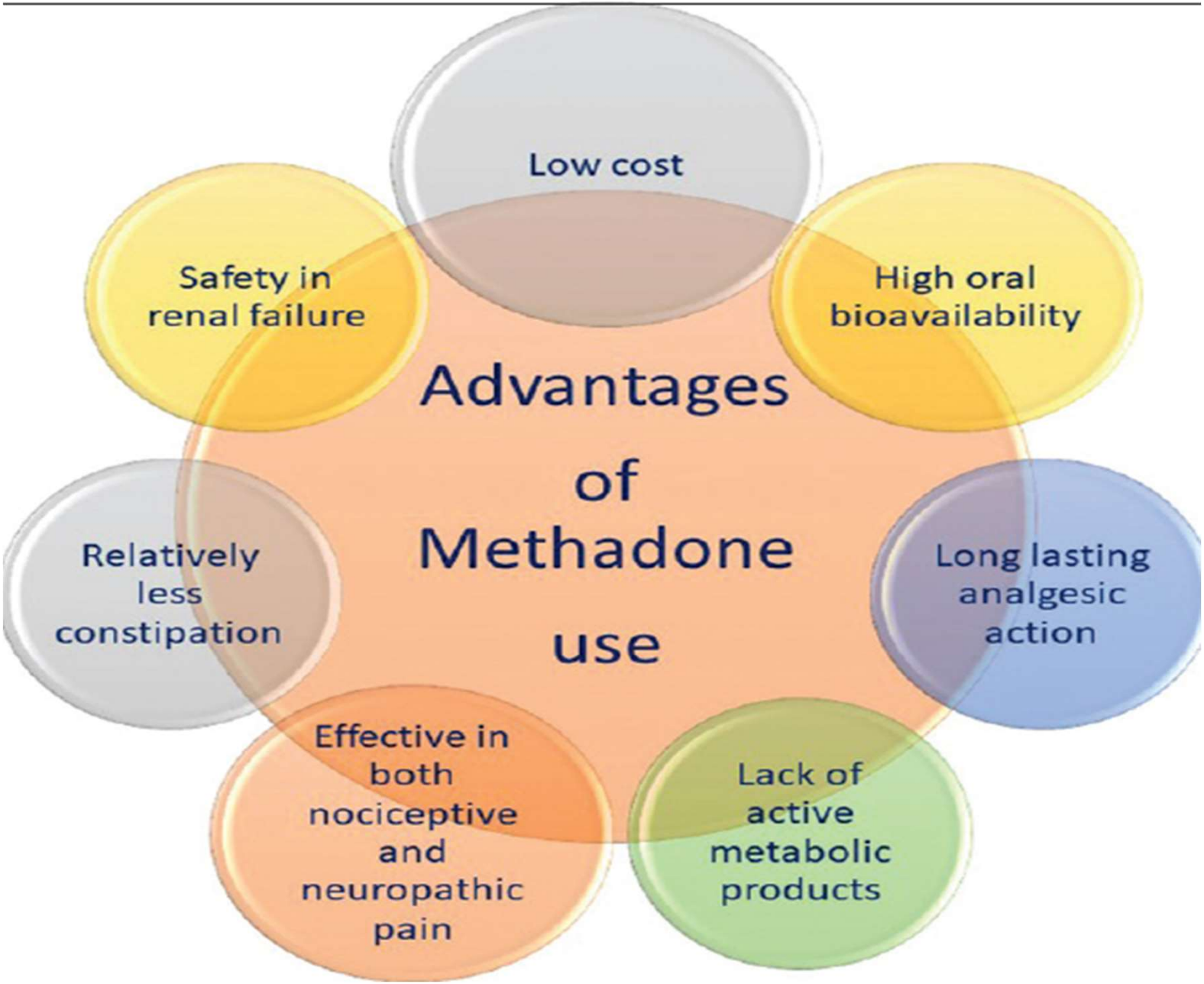
Methadone



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Candidates for Methadone Therapy

- Moderate to severe pain
- Patients with true morphine allergy
- Significant renal impairment
- Presence of neuropathic pain
- Pain refractory to other opioids (high opioid tolerance)
- Cases where cost is an issue
- Patients needing long-acting opioid and are unable to swallow tablets
- Patients exhibiting signs of opioid neurotoxicity

-McPherson ML. Methadone: A complex and challenging analgesic, but it's worth it! Demystifying opioid conversion calculations: A guide for effective dosing. 2nd edition. ASHP, Inc, Bethesda; 2018: 152-153

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When to Avoid Methadone Therapy

- Limited prognosis < 1 week
- Drug-drug interactions
- History of arrhythmias or QTc prolongation
- Lack of caregiver support
- Non-adherence
- Lack of practitioner for continued monitoring

-McPherson ML. Methadone: A complex and challenging analgesic, but it's worth it! Demystifying opioid conversion calculations: A guide for effective dosing. 2nd edition. ASHP, Inc, Bethesda; 2018: 152-153

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Methadone Adverse Effects

Common- **like all opioids**

- Nausea
- Sedation
- Dry mouth
- Constipation

Less common- **like all opioids**

- Sweating
- Pruritus
- Neurotoxicity: myoclonus, delirium
- Respiratory depression
- Sleep apnea
- Serotonin Syndrome

Unique to Methadone

- Significant QT/QTc prolongation

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-Clinical Pharmacology [Internet]. Tampa (FL): Elsevier [Jan 18, 2023]

Methadone in Opioid-Naïve Patients

- Patients receiving up to 40-60 mg oral morphine per day considered opioid-naive
- Hospice and palliative care experts recommend a starting dose of 2 to 7.5mg of oral methadone per day
- Initial dose increases of no more than 5 mg/day every 5-7 days
- Total daily dose (TDD) exceeds 30-40 mg/day, dose increase should be no more than 10 mg/day every 5-7 days

McPherson ML. Methadone: A complex and challenging analgesic, but it's worth it! Demystifying opioid conversion calculations: A guide for effective dosing. 2nd edition. ASHP, Inc, Bethesda; 2018: 153-159

-Chou R, Cruciani RA, et. al. Methadone Safety: A Clinical Practice Guideline From the American Pain Society and College on Problems of Drug Dependence , in Collaboration With the Heart Rhythm Society. *The Journal of Pain.* 2014; 321-337

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Breakthrough Pain Medication with Methadone

- Most practitioners do not use methadone for rescue dosing
- For opioid-naïve patients: morphine 2.5-5mg po every 2-4 hours as needed
- Methadone may be used as a breakthrough regimen when other opioids are contraindicated (i.e, true allergy to all other opioids)
- May administer 10-15% of scheduled methadone TDD every 3 hours as needed
- Note: this is not preferred due to risk of accumulation and unintentional overdose
- Important to keep pain dairy to document use of breakthrough pain medications

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Monitoring and Titration

Monitoring

- It takes several days to achieve full analgesic effect
- Respirations (depth, rhythm, rate)
- Opioid overdose signals (difficulty waking, loud snoring, slurring of speech)
- Cardiac monitoring: Unexplained syncope or seizures

Gradual titration

- Long half-life
- May increase after 5-7 days according to the amount of breakthrough pain medication taken

-McPherson ML. Methadone: A complex and challenging analgesic, but it's worth it! Demystifying opioid conversion calculations: A guide for effective dosing. 2nd edition. ASHP, Inc, Bethesda; 2018: 155-158

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Methadone in Opioid-Tolerant Patients

- Various ratios exist to guide the conversion of opioids such as morphine to methadone
- Not a linear conversion: the higher the morphine equivalents, the higher the methadone potency
- No evidence to support superiority of one conversion method over another
- Converting from other opioids to methadone
  - Step 1: Assess patient
  - Step 2: Determine TDD of current opioid
  - Step 3: Covert to daily oral morphine equivalent, calculate methadone TDD
  - Step 4: Stop original opioid start individualized methadone regimen with the next dose
  - Step 5: Monitor

McPherson ML. Methadone: A complex and challenging analgesic, but it's worth it! Demystifying opioid conversion calculations: A guide for effective dosing. 2nd edition. ASHP, Inc, Bethesda; 2018: 163-164

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Conversion Ratios used by Enclara Pharmacia

OME Daily Dose (mg/day)	Initial Equianalgesic Ratio (M:ME)
< 60	Recommend opioid naïve dosing
60 – 99	4:1
100-299	8:1
300-360	12:1
>360	Recommend TDD of 30mg

Initial recommendations of methadone are limited to 30mg per day regardless of previous opioid usage

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Methadone as an Adjuvant Analgesic in Hospice

- Some evidence exists supporting use of methadone adjunctively to an opioid regimen
- The addition of low-dose methadone may be beneficial in
  - Opioid-induced hyperalgesia
  - Opioid tolerance
  - Opioid resistant neuropathic pain
  - Opioid regimens simply needing boost
- Useful when the patient's life expectancy is shorter than the time to steady state

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Clinical Considerations: Methadone

- Some patients may not reach steady state for over 3 weeks
- Single doses of methadone are effective for about 4 to 8 hours. With chronic dosing, as steady-state approaches, the duration of action lengthens; we must carefully explain to the patient that it takes several days to achieve the full analgesic effect of methadone
- Must always have an effective breakthrough medication
  - 10-15% TDD Morphine Equivalent
- During initiation/titration phase, need close follow up
- Cigarette smoking/cessation can impact serum methadone concentration
- Doses for pain are generally MUCH lower than doses for addiction treatment

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Knowledge Check

TRUE or FALSE
Buprenorphine is a partial mu agonist, so, therefore is not as potent as a full agonist like morphine

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Buprenorphine

- Synthetic opioid shown to be effective for both pain management and opioid use disorder
- Schedule III partial opioid agonist; **however, it does not provide "partial" analgesia**
- Analgesia from buprenorphine is equivalent to full agonists (like morphine, oxycodone, fentanyl)
- Depending on the formulation, buprenorphine is approximately 25-100 times more potent of an analgesic than morphine (which makes it nearly as potent as fentanyl)
- Because buprenorphine does not occupy all the mu opioid receptors, the open receptors remain available for other full agonists (like morphine) to have effect
- Safe for use in mild to moderate liver failure and in renal failure
- High first pass hepatic metabolism results in poor (10-20%) oral bioavailability; transdermal, sublingual, and buccal formulations are typically utilized; buccal provides higher bioavailability than sublingual
- Lower incidence of opioid-like adverse effects, including respiratory depression

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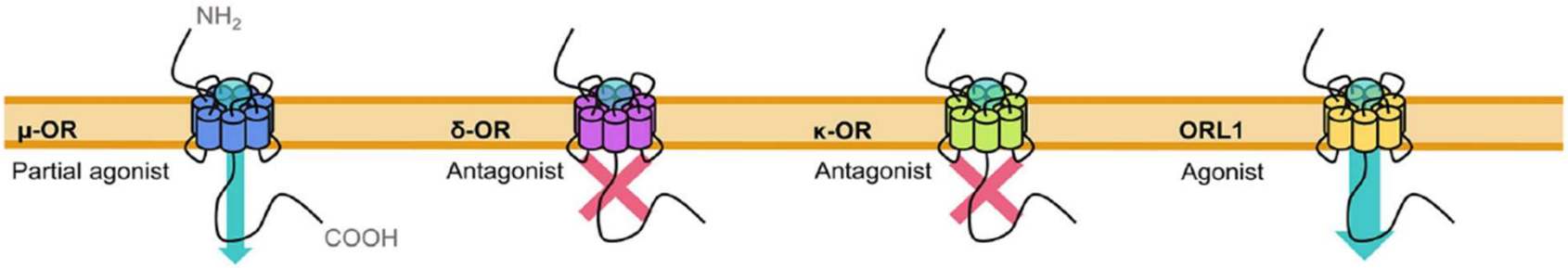
Buprenorphine Receptor Binding



- Potent analgesia
- Ceiling on respiratory depression and euphoria
- Limited impact on GI motility
- Limited physical dependence, abuse potential, and withdrawal symptoms
- Reduced immunosuppression and impact on the HPA axis
- Reduction in suicidal thoughts, anxiety, and depression
- Limited dysphoria

- Anti-opioid effects
- Myocardial protection
- Limited impact on GI motility*
- Limited respiratory depression*

- Reduced depression, dysphoria, suicidal tendencies, anxiety, and hostility
- Limited potential for addiction* and tolerance
- Reduced immunosuppression

- Enhanced spinal analgesia
- Reduced supraspinal analgesia
- Diminished opioid-rewarding effects
- Limited potential for tolerance

Gudin, Jeffrey, and Jeffrey Fudin. "A narrative pharmacological review of buprenorphine: a unique opioid for the treatment of chronic pain." *Pain and Therapy* 9 (2020): 41-54.

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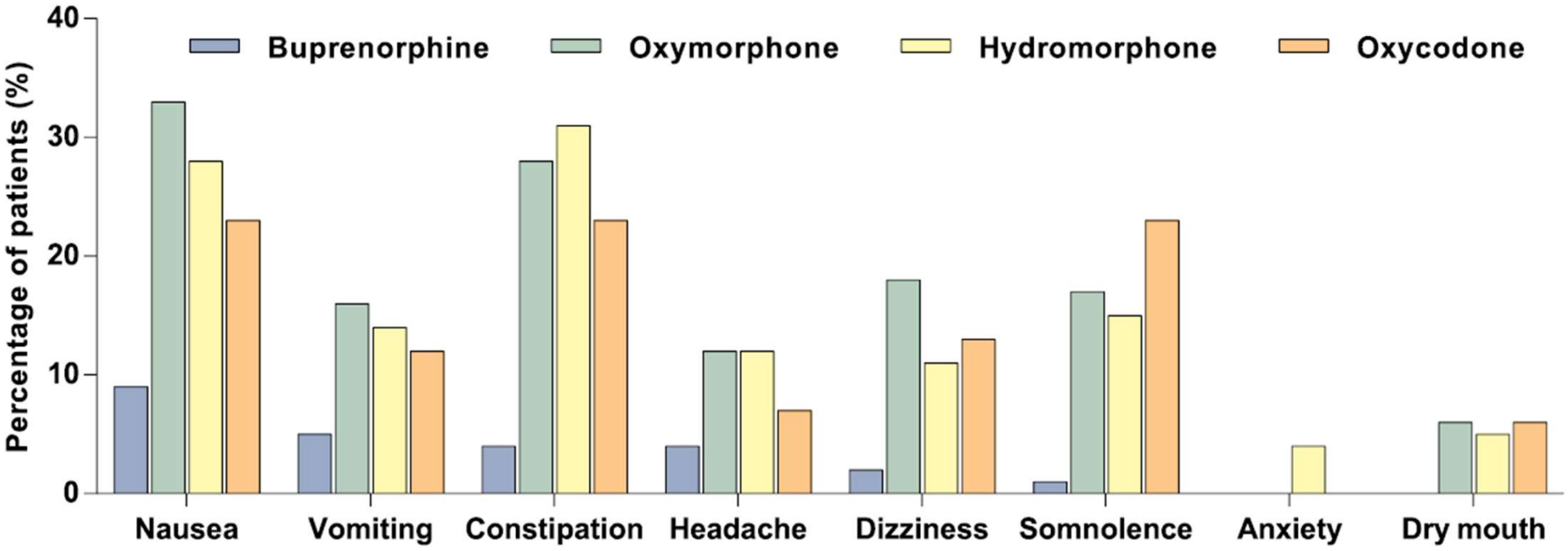
Opioid Adverse Effects Comparison



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Buprenorphine Dosage Forms

Dosage Form	Dosages
Transmucosal Film (Belbuca®)	75, 150, 300, 450, 600, 750, 900 mcg
Transdermal Patch (Butrans®)	5, 7.5, 10, 15, and 20 mcg/h
Sublingual tablet with naloxone (Zubsolv®)	0.7 mg, 1.4 mg, 2.9 mg, 5.7 mg, 8.6 mg, 11.4 mg
Sublingual tablet with naloxone (generic)	2 mg, 8 mg
Sublingual Strip with naloxone (Suboxone®)	2 mg, 4 mg, 8 mg, 12 mg
Sublingual tablet (generic; without naloxone)	2 mg, 8 mg

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Transdermal Buprenorphine

- Better tolerated than sublingual buprenorphine and effective in managing chronic pain
- Available in 5, 7.5, 10, 15, and 20 mcg/h doses and is designed to be applied every 7 days
- Worn continuously for 7 days, with steady state achieved 3 days of continuous applicatio
- **Dose can be adjusted every 3 days (72 hours)**
- After removal of Butrans®, mean buprenorphine concentrations decrease approximately 50% within 10 to 24 hours, followed by a decline with an apparent terminal half-life of approximately 26 hours.
- Need to rotate the application site of the patch, as placing the patch in the same site can lead to increased drug absorption
  - Don't apply patches to same area for 3-4 weeks
- Drug absorption is 26% greater when patches are placed on the upper back as opposed to sides of the chest

OME 7-15 mg/24 hours for 5 mcg patch

OME 30 mg/24 hours for 10 mcg patch

Dalal S, Chitneni A, Berger AA, Orhurhu V, Dar B, Kramer B, Nguyen A, Pruit J, Halsted C, Kaye AD, Hasoon J. Buprenorphine for Chronic Pain: A Safer Alternative to Traditional Opioids. Health Psychol Res. 2021 Aug 6;9(1):27241.
https://butrans.com/delivery/transdermal-patch.html

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Sublingual Buprenorphine

- Tablets that come in several dosages, ranging from 0.7 to 11.4 mg
- Median dissolve time is about 5 minutes
- Plasma concentrations begin within 10-20 minutes; peak drug concentration at 1-2 hours
- Half life 31-36 hours
- Higher incidence of adverse effects than transdermal buprenorphine
- Must be administered whole, cannot be cut, chewed or swallowed
- Don’t eat or drink until completely dissolved
- If a patient needs more than one tab, place all tabs under the tongue at once
- Don’t want to swallow the tabs because that decreases the bioavailability

https://docs.boehringeringelheim.com/Prescribing%20Information/PIs/Roxane/Buprenorphine%20HCl%20Sublingual%20Tabs/10004964_01%20Buprenorphine%20HCl%20Sublingual%20Tabs.pdf

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Buprenorphine Effectiveness

- A systematic review of ten trials involving 1,190 patients demonstrated that sublingual buprenorphine is effective as an analgesic
- 23 out of 24 studies showed buprenorphine is just as effective as morphine, fentanyl, and oxycodone for pain treatment
- May be preferred in elderly patients, since clearance is not affected by age, renal failure

Cote J, Montgomery L. Sublingual buprenorphine as an analgesic in chronic pain: a systematic review. *Pain Med*. 2014;15(7):1171-1178.
Raffa RB, Haidery M, Huang HM, et al. The clinical analgesic efficacy of buprenorphine. *J Clin Pharm Ther*. 2014;39(6):577-583.
Dalal S, Chitneni A, Berger AA, Orhurhu V, Dar B, Kramer B, Nguyen A, Pruit J, Halsted C, Kaye AD, Hasoon J. Buprenorphine for Chronic Pain: A Safer Alternative to Traditional Opioids. Health Psychol Res. 2021 Aug 6;9(1):27241.

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Rotating To/From Buprenorphine

Why is buprenorphine not on the equianalgesic charts?

- Rotating a patient from high-dose full agonist opioids to buprenorphine requires significant planning to minimize the patient experiencing opioid withdrawal and/or worsening pain

- Rotating a patient from buprenorphine to a traditional full agonist opioid requires close monitoring, as the full agonist opioid has a higher risk of respiratory depression than buprenorphine.

Case, Amy A., et al. "Treating Chronic Pain with Buprenorphine—The Practical Guide." *Current Treatment Options in Oncology* 22.12 (2021): 1-13.

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Switching FROM Buprenorphine Patch

1 mg buprenorphine = 75 mg oral morphine (*note this is a general guideline, not to be used like an equipotency chart)*

Remember patches are MICROGRAMS PER HOUR

So…5 ug/hr buprenorphine patch X 24 hrs = 120 ug/day buprenorphine = 0.12 mg/day x 75 mg conversion = 9 mg/day OME.

After removal of Butrans®, mean buprenorphine concentrations decrease approximately 50% within 10 to 24 hours, followed by a decline with an apparent terminal half-life of approximately 26 hours

Starting Buprenorphine: BUTRANS® dosing

- Low to moderate doses (e.g., 5 **mcg**/h patch) can be initiated for pain in patients who are **opioid naïve**
- BUTRANS doses of 7.5, 10, 15, and 20 mcg/hour are only for use in patients who NOT opioid naïve
- It may be possible rotate to TRANSDERMAL buprenorphine directly from other opioids without inducing withdrawal

OME 7-15 mg/24 hours	OME 30 mg/24 hours	OME 48 mg/24 hours
Transdermal buprenorphine 5 mcg/h	Transdermal buprenorphine 10 mcg/h	Transdermal buprenorphine 20 mcg/h

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Rotating TO Buprenorphine from Other Opioids

- Since buprenorphine works on different receptors than other opioids, rotating TO buprenorphine can lead to symptomatic opioid withdrawal when using a “stop/start” approach

- Initial stop-start strategies (no longer favored) in rotating to buprenorphine to avoid withdrawal symptoms consisted of a gap in time between stopping the existing opioid and starting sublingual (SL) buprenorphine (not transdermal).
  - gap interval of 12-25 hours for non-methadone, more than 24 hours for methadone
  - buprenorphine then started, often at onset of withdrawal symptoms and repeated every 1-4 hour

- The risk of inducing withdrawal with a start-stop rotation strategy without a gap is significant if oral morphine equivalents per day (OME) are greater than 120 or methadone greater than 50 mg per day.

- Strategy is difficult, may require hospitalization, and can potentially lead to withdrawal symptoms during the gap, as well as uncontrolled pain

Case, Amy A., et al. "Treating Chronic Pain with Buprenorphine—The Practical Guide." *Current Treatment Options in Oncology* 22.12 (2021): 1-13.

Rotating to Buprenorphine from Other Opioids

- Microdosing or the “Bernese” Strategy
- The current opioid is continued until SL buprenorphine doses are 8–12 mg.
- Buprenorphine gradually blocks the current opioid access to MOR and becomes the primary analgesic or maintenance opioid.
- Withdrawal does not occur when the potent opioid is then abruptly stopped.

Day	Buprenorphine	Schedule II opioid
Day 1	0.5 mg SL daily*	Full dose
Day 2	0.5 mg SL BID*	Full dose
Day 3	1 mg SL BID	Full dose
Day 4	2 mg BID	Full dose
Day 5	4 mg BID	Full dose
Day 6	8 mg qam, 4 mg qpm	Full dose
Day 7	12 mg	Stop

Moe J, et al. Short communication: systematic review on effectiveness of micro-induction approaches to buprenorphine initiation. Addict Behav. 2021;114:106740.

Knowledge Check

TRUE or FALSE
The IV formulation of ketamine can be given orally

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Ketamine

What do I need to know about ketamine for pain?

- Use is off label; evidence on the effect of oral ketamine in chronic pain is limited and the quality of the studies is low
- No commercially available oral formulation; IV fluid can be given orally (bitter taste)
- Low (16-29%) oral bioavailability, significant first-pass effect; initial bioavailability cannot be predicted from patient to patient and thus the effective and safe dose cannot be determined in advance
- Subcutaneous use can cause irritation and pain; most protocols are for continuous subcutaneous injection

Riccardi A, Guarino M, Serra S, Spampinato MD, Vanni S, Shiffer D, Voza A, Fabbri A, De Iaco F; Study and Research Center of the Italian Society of Emergency Medicine. Narrative Review: Low-Dose Ketamine for Pain Management. J Clin Med. 2023 May 2;12(9):3256. Blonk, Maren I., et al. "Use of oral ketamine in chronic pain management: a review." *European journal of pain* 14.5 (2010): 466-472.
Lauretti G.R., Lima I.C., Reis M.P., Prado W.A., Pereira N.L. Oral ketamine and transdermal nitroglycerin as analgesic adjuvants to oral morphine therapy for cancer pain management. *Anesthesiology.* 1999;90:1528–1533. doi: 10.1097/00000542-199906000-00005

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Ketamine for Pain

- Onset of analgesia is 15-30 minutes
- Duration of action is 15 minutes to 2 hours, possibly longer orally
- Side effects at the lower doses used for pain are dose dependent, with dissociative feelings (“spaced out”), nausea, sedation, delirium, and hallucinations reported more frequently with IV administration
- Delusions, memory impairment, dysuria, and abnormal liver functional tests have been associated with therapeutic analgesic doses of just 2 weeks duration

Riccardi A, Guarino M, Serra S, Spampinato MD, Vanni S, Shiffer D, Voza A, Fabbri A, De Iaco F; Study and Research Center of the Italian Society of Emergency Medicine. Narrative Review: Low-Dose Ketamine for Pain Management. J Clin Med. 2023 May 2;12(9):3256. Blonk, Maren I., et al. "Use of oral ketamine in chronic pain management: a review." *European journal of pain* 14.5 (2010): 466-472.
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Ketamine for Pain

- There are no studies comparing various titration or dosing schedules, nor routes of administration
- Usual initial analgesic **oral dose** in adults is 10-25 mg TID to QID with titration in steps of 10-25 mg. The maximum reported oral dose is 200 mg QID
- A common initial **IV dose** in adults is 50-100 mg/day, with titration at increments of 25-50 mg/day, and a usual effective dose of 100-300 mg/day
- Careful monitoring of blood pressure, heart rate, and psychotomimetic effects should occur
- Drowsiness may ensue when patients are on background opioids. Consequently, some clinicians empirically reduce opioid doses by 25-50% when starting IV ketamine

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Riccardi A, Guarino M, Serra S, Spampinato MD, Vanni S, Shiffer D, Voza A, Fabbri A, De Iaco F; Study and Research Center of the Italian Society of Emergency Medicine. Narrative Review: Low-Dose Ketamine for Pain Management. J Clin Med. 2023 May 2;12(9):3256. Blonk, Maren I., et al. "Use of oral ketamine in chronic pain management: a review." *European journal of pain* 14.5 (2010): 466-472.
Lauretti G.R., Lima I.C., Reis M.P., Prado W.A., Pereira N.L. Oral ketamine and transdermal nitroglycerin as analgesic adjuvants to oral morphine therapy for cancer pain management. *Anesthesiology.* 1999;90:1528–1533. doi: 10.1097/00000542-199906000-00005

Drug Interactions with Ketamine

- Any medicine that raises blood pressure or heart rate will increase adverse effects of ketamine

- Strong inhibitors of CYP3A4 may increase ketamine effect –e.g. clarithromycin, ketoconazole (considered less significant for subcutaneous ketamine but may need consideration)

- Strong inducers of CYP3A4 may reduce ketamine effect -e.g. carbamazepine, phenytoin , primidone, rifampin (considered less significant for subcutaneous ketamine but may need consideration)

Riccardi A, Guarino M, Serra S, Spampinato MD, Vanni S, Shiffer D, Voza A, Fabbri A, De Iaco F; Study and Research Center of the Italian Society of Emergency Medicine. Narrative Review: Low-Dose Ketamine for Pain Management. J Clin Med. 2023 May 2;12(9):3256. Blonk, Maren I., et al. "Use of oral ketamine in chronic pain management: a review." *European journal of pain* 14.5 (2010): 466-472.
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Questions?
Thanks!

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