Challenges with Opioids: Adverse Effects and Managing Pain in Patients with Opioid Use Disorder

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Objectives

- Describe several patient-specific factors that can increase the risk of opioid adverse effects
- List the major physiologic systems affected by opioids
- Discuss management strategies for the most common opioid-related adverse effects in hospice and palliative care.
- Define and describe current trends in opioid use disorder (OUD) in hospice and palliative care
- Identify at least four barriers to effective pain management in patients with OUD
- Evaluate the use of methadone and buprenorphine for OUD and pain in hospice and palliative care
- Contrast various patient scenarios for pain management with OUD

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Introduction

- Opioids are commonly used in advanced disease
- Balancing risks and benefits of use
- Contributing factors for adverse effects
  - Drug-related
  - Age-related
  - Disease-related
- Managing refractory symptoms

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Age-Related Attributes

- Physiologic changes
- Comorbidities
- Cognitive impairment
- Organ dysfunction
- More medications
- ADEs present atypically
- Falls and fractures
- Delirium
- Risk of overdose
- Risk of misuse

Pruskowski J, et al. Fast Facts & Concepts #357.May 2018.

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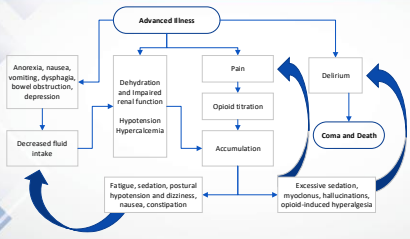
Disease-Related Attributes



Bruera E, ed, et al. Textbook of Palliative Medicine and Supportive Care, 2nd ed. Boca Raton, FL: Taylor & Francis Group, LLC; 2015.

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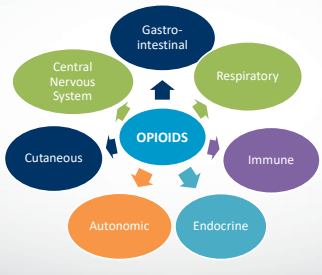
Systems Affected



Bruera E, ed, et al. Textbook of Palliative Medicine and Supportive Care, 2nd ed. Boca Raton, FL: Taylor & Francis Group, LLC; 2015
Portenoy RK, et al. UpToDate. Feb 26, 2019.

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Gastrointestinal
Symptoms include:
Early satiety
Abdominal bloating and cramping
Constipation
Nausea and vomiting
Opioid receptors all along GI tract
Inhibition of gastric emptying
Increased gastric acid secretion
Delay in GI transit
Inhibition of colonic secretions
Affects gallbladder
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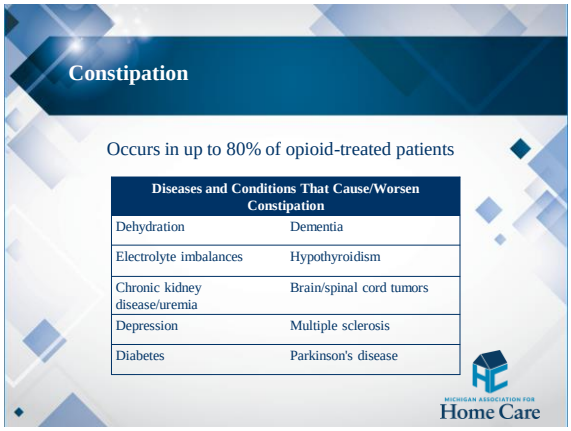
Constipation
Occurs in up to 80% of opioid-treated patients
Diseases and Conditions That Cause/Worsen Constipation
Dehydration
Dementia
Electrolyte imbalances
Hypothyroidism
Chronic kidney disease/uremia
Brain/spinal cord tumors
Depression
Multiple sclerosis
Diabetes
Parkinson's disease
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Medications that Cause/Exacerbate Constipation

Medications That Cause/Exacerbate Constipation	
Medication Type	**Example**
Opioids	Morphine, oxycodone, fentanyl, hydrocodone
Iron, calcium, and/or aluminum	Ferrous sulfate, calcium carbonate, aluminum hydroxide
Antihistamines	Diphenhydramine, chlorpheniramine, meclizine, cetirizine
Diuretics	Furosemide, bumetanide, torsemide, HCTZ
Antidepressants	Amitriptyline, imipramine
Antispasmodics	Tizanidine, cyclobenzaprine
Antihypertensives	Verapamil, amlodipine
Antipsychotics	Chlorpromazine, olanzapine, risperidone, clozapine
Anti-diarrheals	Loperamide
Antiemetics	Ondansetron
Incontinence	Oxybutynin, tolterodine

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Opioid-Induced Constipation

- Opioid-induced constipation is refractory to non-pharmacological methods because opioids bind to receptors in the GI tract and reduce peristalsis.
- For this reason, there is no definitive evidence that measures such as increased hydration, increased fiber intake, or timed toileting are effective in opioid-induced constipation

- Bruera E, ed, et al. Textbook of Palliative Medicine and Supportive Care, 2nd ed. Boca Raton, FL: Taylor & Francis Group, LLC; 2015.
- Rao SSC. Constipation in the older adult. UpToDate. Published May 21, 2018.

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Managing Opioid-Induced Constipation

- Minimize use of other constipating medications
- Evaluate for impaction
- Since opioids reduce peristalsis, need to add a stimulant or osmotic laxative (not a softening agent)

Medication Class	Oral Medication	Starting Dose	Max Daily Adult Dose
Stimulant laxative	Senna tab	1 tab daily or twice daily	8 tabs per day
Stimulant laxative	Bisacodyl	1 tab daily	6 tabs daily (do not crush)
Osmotic laxative	Magnesium hydroxide	15 ml (1200 mg) daily	60ml (4800mg)- total may be divided and given two to 4 times daily
Osmotic laxative	Polyethylene Glycol	17g daily	34 g daily
Osmotic laxative	Lactulose	15 mL daily	60 ml (may divide and give twice a day)
Osmotic laxative	Magnesium Citrate	150 mL daily	300 mL daily (may divide and give twice a day)
Osmotic Laxative	Sorbitol	30 (27 g) daily	45 ml daily

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Laxative Selection/Onset of Action

Up to 6 hours	6-12 hours	1-3 days
• Magnesium citrate (Citroma®) • Magnesium hydroxide (Milk of Magnesia®) • Sodium phosphates (Fleet® oral liquid, enema) • Bisacodyl (rectally) • Sorbitol	• Bisacodyl (oral) • Senna (Senokot®)	• Lactulose • Polyethylene glycol 3350 (Miralax®)

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Chronic Opioid-Induced Constipation

- Chloride channel activator: Lubiprostone (Amitiza®)
  - Increases intestinal fluid secretion, which alters stool consistency and promotes regular bowel movements
  - May not be effective for patients on methadone as methadone reduces its effects
  - Available as an oral capsule
  - Expensive
- Peripherally-acting mu opioid receptor antagonists: Naloxegol (Movantik®), Methylnaltrexone (Relistor®), Naldemedine (Symproic®)
  - Block opioid receptors responsible for constipation without causing significant opioid withdrawal or loss of analgesia
  - Methylnaltrexone: Only the injectable form is approved for the treatment of opioid induced constipation
  - Naloxegol and Naldemedine: Numerous interactions with medications metabolized by the cytochrome P450 system (e.g., proton pump inhibitors, azole antifungals)
  - Expensive

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Opioid-Induced Nausea and Vomiting

- Nausea and vomiting are distressing symptoms and may strongly impact quality of life.
- The incidence of nausea and vomiting in patients treated with opioids for chronic pain in general is 40% (nausea) and 15–25% (vomiting)
- Underlying mechanisms only partly understood but are thought to be
  - 1. Direct stimulation of opioid receptors in the chemoreceptor trigger zone in the brain
  - 2. Binding to opioid-sensitive receptors causing increased vestibular sensitivity
  - 3. Affecting receptors in the gastrointestinal tract

Mallick-Searle T, Fillman M. The pathophysiology, incidence, impact, and treatment of opioid-induced nausea and vomiting. J Am Assoc Nurse Pract 2017;29:704–710

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Managing Opioid- Induced Nausea/Vomiting

- Opioid switch/rotation
- Antiemetics
- Change route of administration

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Opioid Switch/Rotation

- Opioid rotation is where one opioid is exchanged for another to improve pain control or manage certain adverse effects
- Opioids have subtle differences in binding to receptors; the clinical effects can vary from one agent to another
- There are genetic differences in how certain drugs are metabolized
- Clinicians' knowledge of the patient's comorbidities, medication profile, allergies, and past experience with various opioids all play a role when making a switch
- Evidence weakly suggests that morphine and tramadol cause more nausea than oxycodone, codeine, hydrocodone, fentanyl, or methadone

Sande, Tonje A., Barry JA Laird, and Marie T. Fallon. "The management of opioid-induced nausea and vomiting in patients with cancer: a systematic review." *Journal of palliative medicine* 22.1 (2019): 90-97.

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Antiemetics

Antihistamines	Diphenhydramine (Benadryl) 25 to 50 mg orally every four to six hours	These agents more useful if nausea related to ambulation
	Meclizine (Antivert) 12.5 to 25 mg orally every six to eight hours	
Antipsychotics and related agents	Haloperidol (Haldol) 0.5 to 2 mg orally two to four times per day	Multiple uses for haloperidol in palliative medicine
	Prochlorperazine (Compazine) 5 to 10 mg oral every six to eight hours or 25 mg rectally every 12 hours	Prochlorperazine less sedating than promethazine
	Promethazine (Phenergan) 12.5 to 25 mg orally or rectally every four to six hours	Dopamine-blocking properties less than prochlorperazine; more antihistaminic qualities
Prokinetic agents	Metoclopramide (Reglan) 5 to 10 mg orally up to four times per day	Lower doses preferred in older patients; more useful if early satiety is the presenting problem
Serotonin antagonist	Ondansetron (Zofran) 4 mg orally two to four times per day	Rapid disintegrating tablet can be beneficial for patients who cannot tolerate oral meds

Swegle JM, Logemann C. Management of common opioid-induced adverse effects. Am Fam Physician. 2006 Oct 15;74(8):1347-54.

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Other Antiemetic Strategies

- Initiate around-the-clock (ATC) regimen
- Pre-treat opioid dose
- Add non-opioid and/or adjuvant medication to assist in sparing opioid dose

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Change Route of Administration

- Lack of quality data
  - Limited evidence that switch from oral to SQ can decrease nausea
  - Also limited evidence that transdermal delivery of opioids may have less nausea

Sande, Tonje A., Barry JA Laird, and Marie T. Fallon. "The management of opioid-induced nausea and vomiting in patients with cancer: a systematic review." *Journal of palliative medicine* 22.1 (2019): 90-97.

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CBD/Cannabinoids/Cannabis for Opioid N&V

- **Cannabinoids**
  - Dronabinol (Marinol®) is synthetic THC indicated for chemo-related N&V
  - Nabilone (Cesamet®) is a synthetic THC analog and binds to endogenous cannabinoid receptors CB1 and CB2; indicated for chemo-related N&V
- **Cannabis**
  - Legal for medicinal and recreational use in several U.S. states
  - Several RCTs show efficacy as an antiemetic, particularly for chemo-induced nausea
  - Inhalation: immediate onset, easy titration
  - Ingestion: Slow onset, long half-life
  - No specific trials found for use in opioid-induced nausea/vomiting (secondary outcome in some trials has mixed results)
  - Concomitant use can increase sedation; be aware of drug interactions (especially seizure meds)

Smith LA, Azariah F, Lavender VT, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. Cochrane Database Syst Rev. 2015 Nov 12;2015(11):CD009464.

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Transdermal Gels for N&V

- **ABH/ABHR gels**
  - Historically used based on anecdotal benefit
  - Studies show no transdermal absorption
  - No clinical benefits shown in studies evaluating symptoms or vomiting episodes vs. placebo
  - Evidence doesn't support use
  - Alternative routes should be used

AAHPM. Five things physicians and patients should question. 2013; Feb 21. Article link
Fletcher DS, et al. A Randomized Trial of the Effectiveness of Topical "ABH Gel" (Ativan®, Benadryl®, Haldol®) vs.Placebo in Cancer Patients With Nausea. J Pain Symptom Manage. 2014;48(5):797-803.
Smith TJ, Boyer JK, Pokkis JL, et al. ABH gel is not absorbed from the skin of normal volunteers. J Pain Symptom Manage 2012;42(5):961-966.
Bircher J, et al. Lorazepam, diphenhydramine, and haloperidol transdermal gel for rescue from chemotherapy-induced nausea/vomiting: Results of two pilot trials. J Support Oncol. 2008;6(1):27-32.

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Central Nervous System

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Opioid-Induced Cognitive Changes

Sedation		
Transient	→	Persistent
Cognitive Impairment		
Slight inattention or fatigue	→	Disorientation, severe memory impairment, confusion, delirium
Perceptual Disorders		
Dreaming, illusions	→	Hallucinations
Mood Disturbances		
Negative: Irritability, depressed mood, dysphoria	>	Positive: Contentment, euphoria

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Opioid Induced Cognitive Changes

- Often resolve after a few days
- May persist with concomitant medications/comorbidities

Sedating Medications	Comorbidities
• Benzodiazepines (e.g., lorazepam (Ativan®))	• Dementia
• Antipsychotics (e.g., haloperidol (Haldol®), risperidone (Risperdal®)	• Metabolic encephalopathy
• Muscle relaxants (e.g., carisoprodol (Soma®))	• Brain metastases
• Phenobarbital	

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Evaluating Cognitive Changes

- Look at temporal course
  - Did changes coincide with addition or increase of opioid?
- Is there also respiratory depression?
  - Combination of cognitive changes and respiratory depression may indicate opioid overdose

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Managing Opioid-Induced Cognitive Change

- Removal of contributory factors, as feasible
- Evaluation of pain control
  - Dose reduction trial
  - Rotation to another opioid
  - Initiate a co-analgesic to spare opioid dose (e.g., NSAIDs, corticosteroids, antidepressants, anti-seizure meds, anesthetics)
- Palliate sedation with a psychostimulant
  - Limited duration of therapeutic effects
  - Side effects: Tremulousness, insomnia, anorexia, anxiety, ↑BP, ↑HR
  - Most experience: Methylphenidate (Ritalin®), modafinil (Provigil®)
  - Alternatives: Dextroamphetamine (Dexedrine®), dexmethylphenidate (Focalin®), atomoxetine (Straterra®), caffeine

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- Portenoy RK, et al. UpToDate. Feb 26, 2019.
- Kurita, Genzo P., et al. "Prevalence and predictors of cognitive dysfunction in opioid-treated patients with cancer: a multinational study." *Journal of Clinical Oncology* 29.10 (2011): 1297-1303.

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Opioid Induced Neurotoxicity (OIN)

- Symptoms
  - Severe sedation
  - Delirium
  - Hallucinations
  - Myoclonus
  - Seizures
  - Allodynia
  - Hyperalgesia
- Contributory Factors
  - High Dose
  - Rapid dose escalation
  - Older age
  - Renal failure
  - Dehydration
- Active metabolites
  - Codeine
  - Hydrocodone
  - Hydromorphone
  - Meperidine
  - Oxycodone
  - Morphine

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Managing OIN

- 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 (general rule; evaluate patient specific factors)
- Hydration
  - Utilize (if feasible) when the cause of OIN is believed to be related to dehydration
- Adjunctive medications
  - Add medication therapy to treat symptoms of OIN and/or reduce the patient's opioid requirements
  - Myoclonus- consider medications such Ativan® (lorazepam), Klonopin ® (clonazepam), Flexeril ® (cyclobenzaprine)
  - Nonopioid analgesics, such as NSAIDs (e.g., ibuprofen) may help to decrease opioid dose and frequency needs

Kaldor M, Anderson MA, and Sparbel K. Opioid-Induced Neurotoxicity in the Hospice Patient. *Journal of Hospice & Palliative Nursing.* 2011; 13(5): 314-318.

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

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Respiratory

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Opioid Induced Respiratory Depression

- Also called hypoventilation
- Slow, shallow breathing rate of less than 12 breaths per minute
- Rarely an issue with proper opioid titration
- Tolerance develops within days after opioid initiation
- **Risk factors**
  - Opioid-naïve patients administered high opioid doses
  - Morbid obesity
  - Sleep apnea
  - Advanced age
  - Renal failure

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Managing Opioid Induced Respiratory Depression

- Reducing or omitting next opioid dose
- Provide supplemental oxygen
- Administer naloxone
  - Patient difficult to arouse or unarousable
  - Shallow/slow respirations with evidence of inadequate ventilation

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Cutaneous

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Pruritus

- Mild or transient episodes in up to 10% of patients on chronic systemic opioids; higher with intravenous vs. oral opioids.
- Persistent or troublesome pruritus occurs only in approximately 1% of patients
- Generalized and not associated with a rash (although hives can occur).
- Pruritus may be more common with naturally occurring opioids, such as codeine and morphine, although data is conflicting
- Mechanism is uncertain
  - Histamine plays a role for morphine; less so for other opioids
- Distinguish between adverse effect and true allergic reaction
  - True allergic reaction = rash, angioedema, bronchospasm
  - If true allergy, consider an opioid from another structural class

Cherny, Nathan, et al. "Strategies to manage the adverse effects of oral morphine: an evidence-based report." *Journal of Clinical Oncology* 18.9 (2001): 2542-2554.

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Management of Opioid-Induced Pruritis

- Consider switch to different structural class + antihistamine
- Dose reduction may benefit some patients
- Antihistamines (ANY can be used)
  - loratadine (Claritin®), cetirizine (Zyrtec®), fexofenadine (Allegra®)
  - Diphenhydramine (Benadryl®) hydroxyzine (Atarax®, Vistaril®)
- Opioid antagonists reserved for severe cases
  - Naloxone, naltrexone
  - Nalbuphine

Structural Class	Opioid
Morphine	Morphine, codeine, hydrocodone, oxycodone, oxymorphone, hydromorphone
Phenylpiperidines	Meperidine, fentanyl
Phenylpropylamines	Tramadol, tapentadol
Diphenylheptanes	Methadone

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Autonomic

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Urinary Retention

- Peripheral effect on nerves that innervate the bladder
- No preventative strategies

Management

- Bladder catheterization
- Reduce opioid dose and/or discontinue meds with anticholinergic effects
- Low-dose naloxone – decreased analgesia
- Methylnaltrexone, nalbuphine – limited evidence
- Doxasozin (Cardura®), tamsulosin (Flomax®) - anecdotal

Medications with high anticholinergic potency
Antihistamines (diphenhydramine, doxepin, hydroxyzine)
Parkinson's medications (benztropine, trihexyphenidyl)
Medications for overactive bladder (oxybutynin, tolterodine)
Muscle relaxants (tizanidine)
Scopolamine, promethazine
Tricyclic antidepressants (amitriptyline, doxepin)

- Bruera E, ed, et al. Textbook of Palliative Medicine and Supportive Care, 2nd ed. 2015.
- Portenoy RK, et al. UpToDate. Feb 26, 2019.
- Twycross W. Fact Facts and Concepts. #287. Feb 2015.

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Pain Management for Patients with Opioid Use Disorder

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Palliative Care Specialists Series

Feature Editors: Christopher A. Jones and Arif H. Kamal

Top Ten Tips Palliative Care Clinicians Should Know About Opioid Use Disorder

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Current State

- Studies in hospice and palliative care patients reveal a prevalence of substance abuse disorders (SUD) of 25-50%
- Opioids are commonly prescribed for pain and symptom management
- Despite this, many hospices and PC teams lack protocols, approaches, and strategies for managing patients with SUD

Gabbard J, Jordan A, Mitchell J, et al.: Dying on hospice in the midst of an opioid crisis: What should we do now? Am J Hosp Palliat Med 2019;36:273–281.
Childers JW, King LA, Arnold RM: Chronic pain and risk factors for opioid misuse in a palliative care clinic. Am J Hosp Palliat Med 2015;32:654–659.

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What is Opioid Use Disorder (OUD): DSM-5 Criteria

1. Increased amounts of opioids are used or the duration of use is longer than intended
2. Persistent desire or unsuccessful efforts to cut down or control opioid use
3. Excessive time spent in efforts to obtain, use, or recover from opioid use
4. Strong desire, or craving, for opioid use
5. Opioid use despite resultant inability to fulfill obligations
6. Continued opioid use despite interference with personal interactions, social obligations, and/or work
7. Elimination or reduction in activities because of opioid use
8. Continued opioid use despite risk of harm or injury
9. Continued opioid use despite understanding that opioid related physical or psychological problems exist and are caused or worsened by opioid use
10. Increased doses of an opioid are needed to achieve the effect previously achieved with a smaller dose (tolerance)
11. Symptoms of withdrawal occur when opioid dose is decreased (withdrawal)

Two or more

Within a year

MILD (2-3)----------Moderate (4-5)----------Severe

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What is Opioid Use Disorder

- "A chronic neurobiological disease with genetic, psychosocial, and environmental risk factors and a course that can include relapses and remissions"
- Involves " reprogramming of neuronal circuits involved in pathologic pleasure and stress response, executive functioning, and motivation and inhibition, noting that habit formation occurs with repetitive learned behavior, which is ultimately also influenced by genetics, development, and the environment."
- Human and animal studies clearly demonstrate physical, chemical, and functional brain alterations in SUDs
- Untreated OUD can increase suffering and unintentional death

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Watch Our Language

- The American Medical Association, American Society of Addiction Medicine (ASAM), and addiction literature have called for providers to reduce stigma surrounding SUDs
- Person-first language humanizes patients and shifts public perception by upholding that OUD is a chronic, yet treatable, disease rather than a moral failing
- In multiple studies, participants were more likely to have negative attitudes toward patients described as addicts or substance abusers compared with "persons with SUDs," with the former patients being culpable and punishable

USE	AVOID
Use (illicit) or misuse (prescribed)	Abuse
Positive or negative	Clean or dirty
Persons with SUD, OUD	Addict, substance abuser, junkie, drug seeker

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Medication Assisted Therapy (MAT)

- Effective treatment for OUD, shown to increase treatment retention while decreasing opioid use AND mortality
- Methadone, buprenorphine are commonly used
  - Suppress cravings, but do not provide consistent analgesia when used as prescribed for MAT due to their pharmacokinetics
- Dosed once daily for MAT; dosed multiple times daily for pain
- Pain doses generally much lower than MAT doses
- Abrupt cessation can precipitate opioid withdrawal
- Patients on MAT develop cross tolerance to opioids and may need more frequent/higher opioid doses for effective analgesia
- Stopping buprenorphine and then restarting it later is challenging, as it requires withdrawal of other opioid before induction (or use of micro-dosing strategies)
- Stopping MAT poses risk of relapse, opioid overdose, and death
- Current recommendations are to continue MAT when hospitalized

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Team Approach for Persons with OUD

- Psychological, existential, and spiritual distress increase the risk of OUD
- Complex social situations
- Nonpharmacologic approaches can be helpful
- Effective pain management is essential

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Pain Management for Persons with OUD

- Many hospice and palliative care providers feel ill-prepared to manage OUD and pain
- No widely accepted guidelines on managing SUD/OUD in palliative care/hospice

And yet…

Managing suffering associated with serious illnesses is our job in hospice/palliative care

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Barriers to Success

- **Individual Concerns**
  - Fear of stigma, labeling
  - Fear of relapse
  - Fear of under-treated pain
- **Provider Concerns**
  - 69% concerned about addiction in those with cancer
  - 63% concerned about under-treatment of pain in those with OUD
  - 23-35% feel adequately knowledgeable and confident
  - Perceived/actual difficulty in prescribing medications

Arthur, J., Lu Z., Hui D., Feliman B., Bruera E. Health care provider attitudes, beliefs, and perceived confidence in managing patients with cancer pain and nonmedical opioid use. J Pain Symptom Management. 2021; 61(1): 128-135

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Methadone: General Properties

- Synthetic opioid developed over 80 years ago
- Mu-opioid receptor agonist, also binds to kappa- and delta- opioid receptors
- Inhibits the reuptake of serotonin and norepinephrine
- N-methyl-D-aspartate (NMDA) receptor antagonist
- Routes of administration include oral, rectal, IV & SQ
- Oral tablets available as 5 and 10mg tablets; oral solution available as 5mg/5ml, 10mg/5ml and 10mg/ml
- Fat soluble, is quickly and widely distributed throughout the body, retained in tissues and slowly released back into plasma during redistribution and elimination
- Binds to alpha 1-acid glycoprotein, albumin and globulin

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: 148

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Methadone: General Properties

- Metabolism takes place primarily in the liver - cytochrome P450 enzymes responsible for metabolism include CYP 3A4, 2B6, 2C8, 2C19 and 2D6
- Inactive metabolites of methadone are eliminated in the urine and feces
- Long elimination half-life, ranging from 5 to 130 hours, with average of 20 to 35 hours
- Steady state concentration achieved in 4-10 days
- Multiple medications cause significant drug interactions
- Medications that induce (speed up or increase) or inhibit (slow down or decrease) metabolism of methadone do so by affecting one of these enzymes
- Generally given once daily to reduce opioid craving/prevent withdrawal

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: 149

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Methadone Adverse Effects

- Common- **like all opioids**
  - Nausea
  - Sedation
  - Dry mouth
  - Constipation
- Less common- **like most opioids**
  - Sweating
  - Pruritis
  - Neurotoxicity: myoclonus, delirium
  - Respiratory depression
  - Sleep apnea
  - Serotonin effects
- Unique to Methadone
  - Significant QT/QTc prolongation

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

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Concomitant Treatment of OUD and Pain: Methadone

- Continue OUD dosing as-is, and provide other opioid/nonopioids for long acting and breakthrough
- Divide total daily dose of methadone into three times a day dosing and provide PRNs for breakthrough
  - Avoid using methadone for breakthrough (PRN)due to risk of accumulation/toxicity

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But wait…

What about the patient who was getting methadone from an OUD clinic and now can't get to the clinic?

2021 Expert Panel Consensus document recommends

Change existing methadone dose to every 8-12 hours (may want to decrease total daily dose)

Example: patient enters hospice care from methadone clinic, receiving 60 mg of methadone per day; patient no longer able to go to methadone clinic. Prognosis is weeks to months

Recommendation: Change methadone to 10 every 8 hours, and use morphine for breakthrough pain, titrate methadone every 5-7 days . **This can be prescribed by hospice physician "for pain"**

Merlin, Jessica S., et al. "Expert panel consensus on management of advanced cancer–related pain in individuals with opioid use disorder." *JAMA network open* 4.12 (2021): e2139968-e2139968.

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Buprenorphine

- Synthetic opioid that has been shown to be effective for both pain management and opioid use disorder (OUD)
- 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)
- Safe for use in mild to moderate liver failure and in renal failure
- Dosages for chronic pain are much lower than those for OUD (which is generally in the range of 12-24 **mg**/day)

Sittl R, Nuijten M, Nautrup BP. 2006. Patterns of dosage changes with transdermal buprenorphine and transdermal fentanyl for the treatment of noncancer and cancer pain: a retrospective data analysis in Germany.*Clin Ther*. 28:1144–54.
Schoeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. *Eur J Clin Pharmacol*. 2008;64(12):1147–61.

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Buprenorphine: Unique Properties

- Buprenorphine has effects at several different types of receptors, which gives buprenorphine some unique properties
  - Mu receptor partial agonist: high affinity and slow dissociation provides prolonged pain relief; partial agonism provides a "ceiling effect" for respiratory depression, euphoria, and constipation but does NOT provide a ceiling effect on analgesia
  - Kappa and delta receptor antagonist: potential antidepressant effects, blunted dysphoria and opioid craving effects, decreased incidence of sedation, and anti-hyperalgesia effect
- Because buprenorphine does not occupy all the mu opioid receptors, the open receptors remain available for other full agonists (like morphine) to have effect

Davis, Mellar P., Gavril Pasternak, and Bertrand Behm. "Treating chronic pain: an overview of clinical studies centered on the buprenorphine option." *Drugs* 78.12 (2018): 1211-1238.

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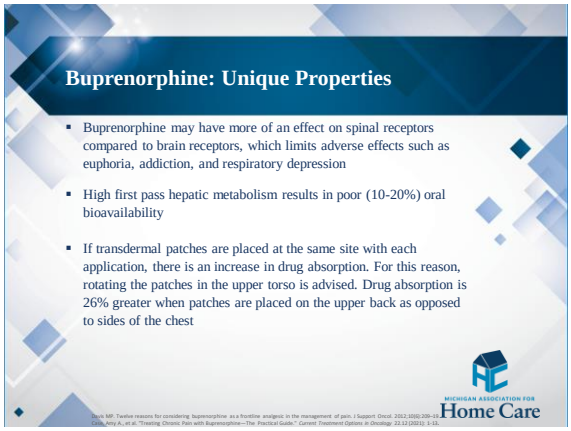
Buprenorphine: Unique Properties
Buprenorphine may have more of an effect on spinal receptors compared to brain receptors, which limits adverse effects such as euphoria, addiction, and respiratory depression
High first pass hepatic metabolism results in poor (10-20%) oral bioavailability
If transdermal patches are placed at the same site with each application, there is an increase in drug absorption. For this reason, rotating the patches in the upper torso is advised. Drug absorption is 26% greater when patches are placed on the upper back as opposed to sides of the chest
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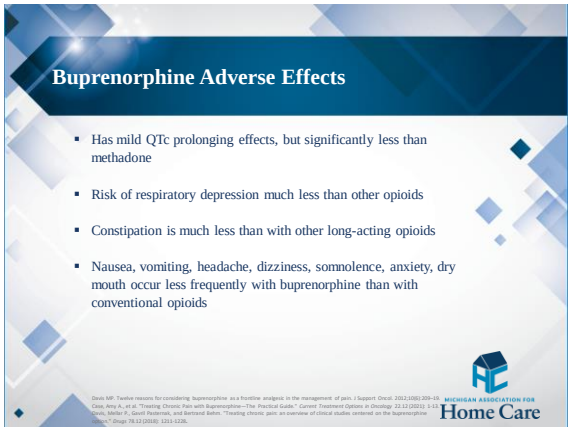
Buprenorphine Adverse Effects
Has mild QTc prolonging effects, but significantly less than methadone
Risk of respiratory depression much less than other opioids
Constipation is much less than with other long-acting opioids
Nausea, vomiting, headache, dizziness, somnolence, anxiety, dry mouth occur less frequently with buprenorphine than with conventional opioids
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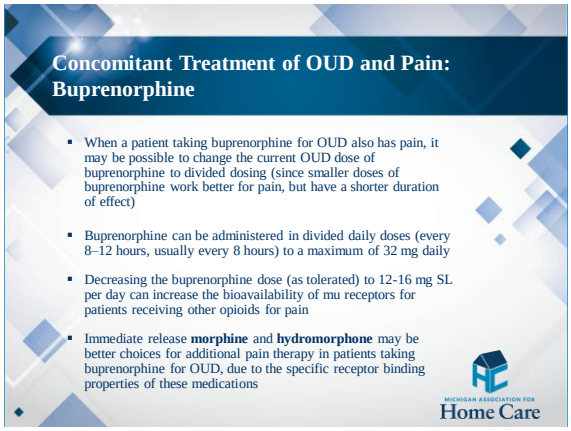
Concomitant Treatment of OUD and Pain: Buprenorphine
When a patient taking buprenorphine for OUD also has pain, it may be possible to change the current OUD dose of buprenorphine to divided dosing (since smaller doses of buprenorphine work better for pain, but have a shorter duration of effect)
Buprenorphine can be administered in divided daily doses (every 8–12 hours, usually every 8 hours) to a maximum of 32 mg daily
Decreasing the buprenorphine dose (as tolerated) to 12-16 mg SL per day can increase the bioavailability of mu receptors for patients receiving other opioids for pain
Immediate release morphine and hydromorphone may be better choices for additional pain therapy in patients taking buprenorphine for OUD, due to the specific receptor binding properties of these medications
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Buprenorphine

- Low to moderate doses (e.g. 5 **mcg**/h) can be initiated for pain in patients who are opioid naïve
- Transmucosal film and transdermal patch have FDA indication for pain; sublingual tablets have FDA indication for OUD and may be used off-label for pain
- Transdermal patch and transmucosal film may not be appropriate for patients on high doses (>190 mg oral morphine equivalent per day) of other opioids
- **Beware of Dosing!** 150 mcg transmucosal film given twice daily produces plasma levels similar to the 10 mcg/h transdermal patch; the 300 mcg transmucosal film is similar to the 20 mcg/h transdermal patch
- As of 12/29/2022, no longer requires X waiver to prescribe for opioid use disorder or a "for pain" designation on prescription when used for pain

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Davis MP. Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. J Support Oncol. 2012;10(5):209–19.

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Buprenorphine Dosage Forms

Dosage Form	Dosages	Notes
Transmucosal Film (Belbuca®)	75, 150, 300, 450, 600, 750, 900 mcg	Specially formulated to improve absorption via a backing that ensures a unidirectional flow of buprenorphine; Do not cut/chew/swallow strip
Transdermal Patch (Butrans®)	5, 7.5, 10, 15, and 20 mcg/h	Peak plasma concentrations are achieved after 72 hours, allowing for dose adjustments every 3 days Drug half-life after removing patch is 12-36 hours; Patch is replaced every seven days
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 (without naloxone)	2 mg, 8 mg	

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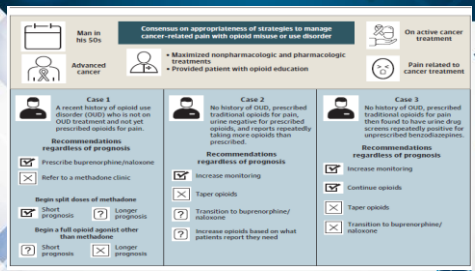
Patients with OUD not on MAT



Fitzgerald Jones K, Khodyakov D, Arnold R, Bulls H, Dao E, Kapo J, Meier D, Paice J, Liebschutz J, Ritchie C, Merlin J. Consensus-Based Guidance on Opioid Management in Individuals With Advanced Cancer-Related Pain and Opioid Misuse or Use Disorder. JAMA Oncol. 2022 Aug 1;8(8):1107-1114

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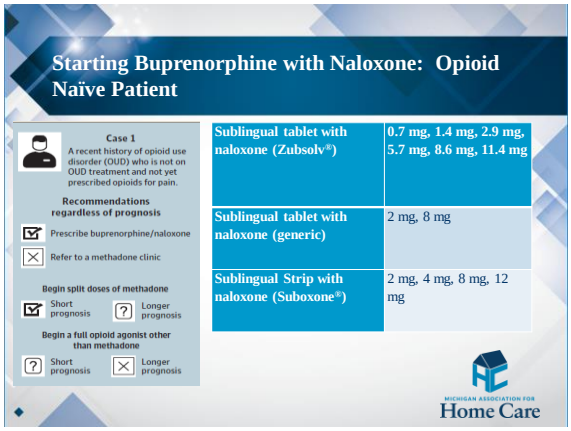
Starting Buprenorphine with Naloxone: Opioid Naïve Patient
Case 1
A recent history of opioid use disorder (OUD) who is not on OUD treatment and not yet prescribed opioids for pain.
Recommendations regardless of prognosis
Prescribe buprenorphine/naloxone
Refer to a methadone clinic
Begin split doses of methadone
Short prognosis
Longer prognosis
Begin a full opioid agonist other than methadone
Short prognosis
Longer prognosis
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
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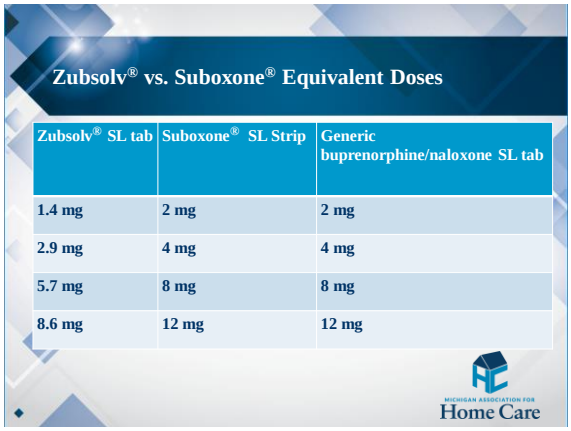
Zubsolv® vs. Suboxone® Equivalent Doses
Zubsolv® SL tab
Suboxone® SL Strip
Generic buprenorphine/naloxone SL tab
1.4 mg
2 mg
2 mg
2.9 mg
4 mg
4 mg
5.7 mg
8 mg
8 mg
8.6 mg
12 mg
12 mg
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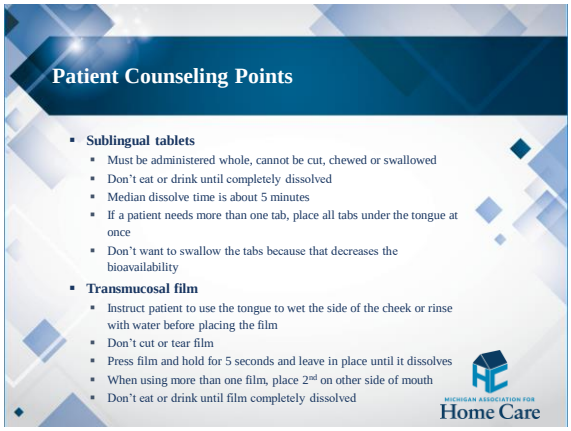
Patient Counseling Points
Sublingual tablets
Must be administered whole, cannot be cut, chewed or swallowed
Don't eat or drink until completely dissolved
Median dissolve time is about 5 minutes
If a patient needs more than one tab, place all tabs under the tongue at once
Don't want to swallow the tabs because that decreases the bioavailability
Transmucosal film
Instruct patient to use the tongue to wet the side of the cheek or rinse with water before placing the film
Don't cut or tear film
Press film and hold for 5 seconds and leave in place until it dissolves
When using more than one film, place 2nd on other side of mouth
Don't eat or drink until film completely dissolved
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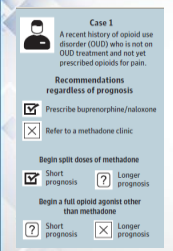
Case 1: Starting Methadone in an Opioid Naïve Patient



- Patients receiving up to 40-60 mg oral morphine per day for less than a week are considered opioid-naïve
- 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
- *What to use for breakthrough?*

McPherson ML, Walker KA, Davis MP, Bruera E, Reddy A, Pace J, Malotte K, Lockman DK, Wellman C, Salpeter S, Bemben NM, Ray JB, Lapointe BJ, Chou R. Safe and Appropriate Use of Methadone in Hospice and Palliative Care: Expert Consensus. White Paper. J Pain Symptom Manage. 2019 Mar;57(3):635-645.e4.

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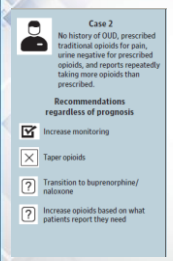
Case 2: Switch to buprenorphine with naloxone



	Oral Morphine Equivalent (OME) /24 hours							
	12 mg	24 mg	48 mg	60 mg	80 mg	100 mg	150 mg	300 mg
Sublingual tablets	n/a	n/a	n/a		1 mg twice daily		1 mg three times daily	2 mg three times daily

Zubsolv® SL tab	Suboxone® SL Strip	Generic buprenorphine/naloxone SL tab
1.4 mg	2 mg	2 mg
2.9 mg	4 mg	4 mg
5.7 mg	8 mg	8 mg
8.6 mg	12 mg	12 mg

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Oral Morphine Equivalents for Buprenorphine

Buprenorphine	Oral Morphine Equivalent (OME) /24 hours							
	12 mg	24 mg	48 mg	60 mg	80 mg	100 mg	150 mg	300 mg
Transdermal patch (Butrans®)	5 mcg/h every 7 days	10 mcg/h every 7 days	20 mcg/h every 7 days		n/a	n/a	n/a	n/a
Transmucosal film (Belbuca®)	75 mcg daily	75 mcg every 12 hours	150 mcg every 12 hours		300 mcg every 12 hours		450 mcg every 12 hours	n/a
Sublingual tablets	n/a	n/a	n/a		1 mg twice daily		1 mg three times daily	2 mg three times daily

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Any Questions?
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Thank You!
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