SAME BUT DIFFERENT: BUPRENORPHINE FOR PAIN AND OUD

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LEARNING OBJECTIVES

- Discuss the clinical interface between pain and addiction
- Differentiate the pharmacology of buprenorphine in comparison to other opioids commonly used in clinical practice
- Given patient-specific information, develop a treatment plan that includes the use of buprenorphine for a patient with chronic pain, OUD, or both

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EPIDEMIOLOGY OF CHRONIC PAIN

- **Rates of chronic pain high in US adults**
  Incidence rate of chronic pain was 52.4 per 1000 person-years in 2019-2020 survey
- **Persistent pain common among those with chronic pain**
  462 per 1000 person-years among those with baseline chronic pain
- **High burden of chronic pain**
  High rates of incidence and persistence emphasize chronic pain burden

These data show chronic pain is common and often persistent in US adults, representing a major health burden.

Nahin RL, et al. JAMA Netw Open. 2023;6(6):e2313563

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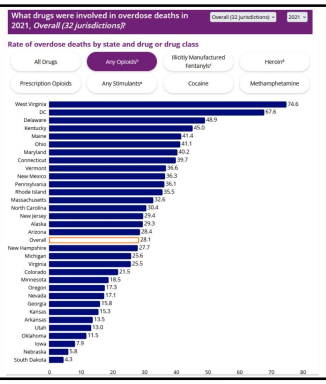
U.S. FATAL OVERDOSE DATA

Centers for Disease Control and Prevention, State Unintentional Drug Overdose Reporting System (SUDORS) Final Data. Atlanta, GA: US Department of Health and Human Services, CDC; Access at: https://www.cdc.gov/drugoverdose/fatal/dashboard



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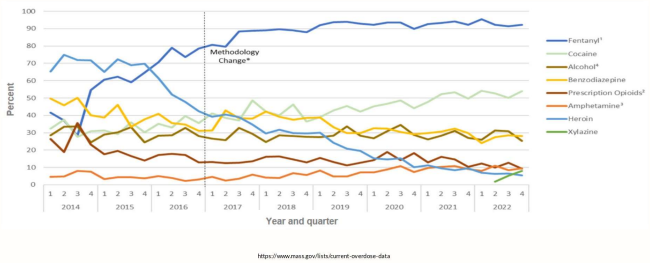
PERCENT OF OPIOID-RELATED OVERDOSE DEATHS BY DRUG TYPE IN MA: 2014-2022



https://www.mass.gov/lists/current-overdose-data

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ADDRESSING DISPARITIES IN THE OPIOID OVERDOSE CRISIS

The opioid crisis in Massachusetts continues to impact communities of color disproportionately. While opioid overdose deaths increased 2.5% overall in 2022, the largest surge occurred among non-Hispanic Black residents. In response, the state is implementing a multifaceted approach focused on treatment, prevention, recovery and addressing systemic issues like housing, employment and mental healthcare access.

https://www.mass.gov/news/massachusetts-opioid-related-overdose-deaths-rose-25-percent-in-2022

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COMMON THREADS: PAIN AND ADDICTION

- Pain and OUD share common neurophysiologic properties
- Genetic and environmental factors contribute to and influence development and course

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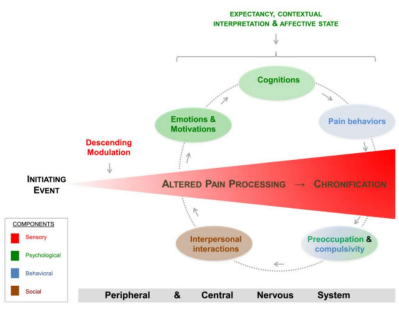
EVOLUTION OF A CHRONIC PAIN SYNDROME

Elman I, Borsook D. Common Brain Mechanisms of Chronic Pain and Addiction. Neuron. 2016;89(1):11-36. doi:10.1016/j.neuron.2015.11.027



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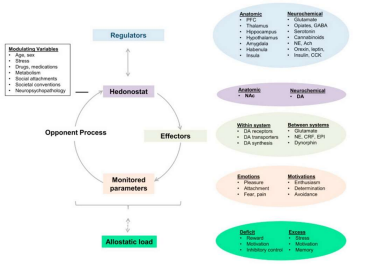
ADDICTION - AN ALLOSTATIC STATE

Elman I, Borsook D. Common Brain Mechanisms of Chronic Pain and Addiction. Neuron. 2016;89(1):11-36. doi:10.1016/j.neuron.2015.11.027



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CHALLENGES OF PAIN MANAGEMENT IN PATIENTS WITH OUD

- High rates of co-occurring psychiatric disorders
- Greater risk for concerning medication-related behaviors
- Increased use of high-cost health care resources

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CONSEQUENCES OF UNTREATED OR UNDER-TREATED PAIN


Neuropsychiatric issues


Psychosocial problems


Disability


Stress and related complications

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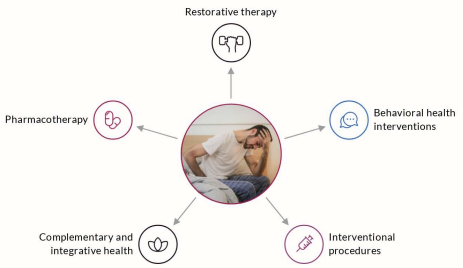
APPROACH TO PAIN MANAGEMENT



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ROLE OF OPIOIDS IN PAIN MANAGEMENT

- **Pain Management**
  Opioids can effectively reduce acute and chronic pain when used properly under medical supervision.
- **Risks**
  Opioids carry risks like addiction, overdose and other side effects.
- **Guidelines and recommendations**
  Following prescribing guidelines can minimize risks and ensure opioids are used appropriately.
- **Alternatives**
  Consider non-opioid therapies and multimodal approaches to pain management when possible.

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ROLE OF BUPRENORPHINE FOR PAIN AND OPIOID USE DISORDER

Partial opioid agonist
Buprenorphine binds to and activates opioid receptors, but not to the same degree as full agonists like morphine.

Ceiling effect on respiratory depression
Unlike full opioid agonists, buprenorphine's partial agonist effects plateau, reducing overdose risk.

Relieves pain and reduces cravings/withdrawal
By activating opioid receptors, buprenorphine can treat pain and opioid dependence, but with less euphoria and abuse potential.

Buprenorphine provides opioid effects that can relieve pain or treat addiction, but with a better safety profile compared to full agonists.

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PHARMACODYNAMICS OF BUPRENORPHINE

Partial mu-opioid receptor agonist
Potent analgesia
Ceiling on respiratory depression

Delta-opioid receptor antagonist
Anti-opioid effects
Reduced opioid adverse effects

Kappa-opioid receptor antagonist
Anti-opioid effects
Reduced dysphoria, hyperalgesia, and immunosuppresion

G-protein signaling, reduced β-arrestin recruitment, and ceiling effect on phosphorylation determine balance between analgesia and adverse effects

Opioid-*receptor*-like 1 (ORL1) agonist
Enhanced spinal analgesia
Diminished opioid reward
Limited potential for tolerance

Weak inhibitor of 5-HT and NE reuptake
Enhanced pain modulation

Voltage-gated sodium channel blocker
Reduced neuronal hyperexcitability

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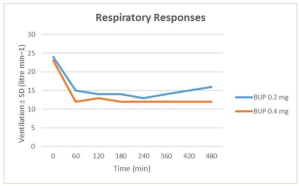
"CEILING" EFFECTS OF BUPRENORPHINE



Dahan A et al. Br J Anaesth 2006; 96 (5): 627-32

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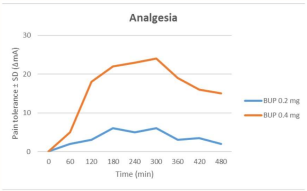
"CEILING" EFFECTS OF BUPRENORPHINE



Dahan A et al. Br J Anaesth 2006; 96 (5): 627-32

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PHARMACOKINETICS OF BUPRENORPHINE

- **Bioavailability**
  Bioavailability varies significantly between formulations
- **Absorption**
  Poor oral absorption due to significant first-pass metabolism
- **Distribution**
  High lipophilicity, low molecular weight, high plasma protein binding
- **Onset and Duration**
  Onset varies by formulation
  Average duration of analgesia is ~6-8 hours
- **Metabolism**
  Does not exhibit linear dose-proportionality over the dose range of 4–32 mg
  Active metabolites
- **Excretion**
  Limited hepatic and renal excretion

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PHARMACOKINETIC COMPARISON OF SELECT BUPRENORPHINE FORMULATIONS

Route of Administration	Bioavailability	Duration of Action	Half-Life (hours)
Parenteral injection	100%	4-6 hrs (single dose) 6-24 hrs (multiple doses)	1.2-7.2
Buccal film	46-65%	12 hrs	24-48
Sublingual tablet and film	28-51%	6-8 hrs	24-42
Transdermal patch	15%	7 days	24-48

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BUPRENORPHINE MONOPRODUCTS

	Brand Name	Formulation	Strengths	Frequency	Label Indications
	Generic Buprenorphine (GENERIC)	SL tablet	(bup/nal): 2mg/0.5mg, 8mg/2mg	Daily to multiple times per day	Opioid Dependence
	Belbuca Buprenorphine (GENERIC)	Buccal Film	75mcg, 150mcg, 300mcg, 450mcg, 600mcg, 750mcg, 900mcg	Daily to multiple times per day	Pain
	Butrans Buprenorphine (GENERIC)	Transdermal	5mcg/hr, 7.5mcg/hr, 10mg/hr, 15mcg/hr, 20mg/hr	Every 7 days	Pain
	Buprenex Buprenorphine (GENERIC)	Injection (IV, IM)	0.3 mg/ml	Multiple times per day	Pain
	Sublocade Buprenorphine XR	Subcutaneous injection	100mg/0.5ml syringe, 300mg/1.5mg syringe	Every 26-30 days	Moderate-Severe OUD
	Brixadi (NDA) Buprenorphine XR	Subcutaneous injection	Weekly: 8mg, 16mg, 24mg, 32mg Monthly: 64mg, 96mg, 128mg	Weekly or monthly	Moderate-Severe OUD

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BUPRENORPHINE-NALOXONE COMBINATION PRODUCTS

	Brand Name	Formulation	Strengths	Frequency	Label Indications
	Generic Buprenorphine & naloxone (GENERIC)	SL tablet	(bup/nal): 2mg/0.5mg, 8mg/2mg	Daily to multiple times per day	Opioid Dependence
	Generic Buprenorphine & naloxone (GENERIC)	Buccal/SL Film	(bup/nal): 2mg/0.5mg, 4mg/1mg, 8mg/2mg, 12mg/3mg	Daily to multiple times per day	Opioid Dependence
	Zubsolv Buprenorphine & naloxone	SL tablet	(bup/nal): 0.7mg/0.18mg, 1.4mg/0.36mg, 2.9mg/0.71mg, 5.7mg/1.4mg, 8.6mg/2.1mg, 11.4mg/2.9mg	Daily to multiple times per day	Opioid Dependence
	Suboxone Buprenorphine & naloxone (GENERIC)	Buccal/SL Film	(bup/nal): 2mg/0.5mg, 4mg/1mg, 8mg/2mg, 12mg/3mg	Daily to multiple times per day	Opioid Dependence

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BUPRENORPHINE WARNINGS AND PRECAUTIONS

Opioid-Specific

- CNS/respiratory depression
- GI dysfunction
- Misuse and addiction
- Hypotension
- Increased intracranial pressure
- Neonatal withdrawal syndrome
- Accidental exposure/overdose

Buprenorphine-Specific

- Application/injection site reactions
- CYP3A4 inhibitors or inducers
- QTc prolongation
- Hepatitis

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BENEFITS OF BUPRENORPHINE FOR OUD

- **Decreased risks of mortality**
  Over 50% lower risk of all-cause and overdose-related mortality
- **Lower rates of opioid misuse**
  Lower rates of other opioid use including injection and cravings
- **Reduced infections**
  Reduced risk of HIV and hepatitis C infections
- **Improved access**
  Increased access leads to decreased opioid overdose deaths
- **Better functioning**
  Improved social functioning and quality of life
- **Maternal benefits**
  Improved maternal and fetal outcomes, less severe neonatal withdrawal

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BUPRENORPHINE FOR ACUTE PAIN

Study	Methods	Outcomes
White et al 2018 (n=2210)	Systematic review & meta-analysis comparing buprenorphine (various formulations) vs. morphine	Pain at 1 hour: WMD=-0.29 (95% CI -0.62-0.03; P=0.07) Respiratory depression: OR=2.07 (95% CI 0.78-5.51; P=0.14) Sedation: OR=1.44 (95% CI 0.76-2.74; P=0.26) Pruritus: OR=0.31 (95% CI 0.12-0.84; P=0.02)
Vlok et al 2019 (n=826)	Systematic review & meta-analysis comparing sublingual buprenorphine vs. IV or IM morphine	Pain at 1 hour: WMD=0.36 (95% CI -0.32-1.05; P=0.30) 3 hours (P<0.0001) 6 hours (P=0.008) Respiratory depression: OR=0.95 (0.48-1.89; P=0.89)

CI – confidence interval; IM – intramuscular; IV – intravenous; OR – odds ratio; WMD – weighted mean difference

White LD et al. Br J Anaesth 2018;120(4): 668e678
Vlok R et al. Am J Emerg Med 2019; 37:381-386

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USE AND RISKS OF BUPRENORPHINE FOR ACUTE PAIN

- Case studies of buprenorphine-associated opioid-induced ventilatory impairment (OIVI)
  Six case studies are analyzed where patients experienced OIVI after taking buprenorphine
- Need for caution and monitoring
  Caution is emphasized when prescribing buprenorphine, especially in elderly, opioid-naïve patients and those on other CNS depressants. Regular monitoring is critical to mitigate risk.

Richards S, Torre L, Lauther B. Anaesth Intensive Care. 2017;45(2):256-261.

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BUPRENORPHINE FOR CHRONIC NONCANCER PAIN

Buprenorphine reduced pain in chronic noncancer pain
Buprenorphine was associated with small but statistically significant reduction in pain scores compared to placebo

Effective for chronic low back pain
Subgroup analyses showed positive analgesic effect when given for chronic low back pain

Transdermal and buccal routes effective
Subgroup analyses showed positive analgesic effect when given via the transdermal and buccal routes

Effective in short and long follow-ups
Subgroup analyses showed positive analgesic effect with follow-up lengths less than and more than 12 weeks

Buprenorphine given transdermally or buccally can reduce chronic noncancer pain, especially for low back pain regardless of follow-up duration.

Weng SC, et al. Anesth Analg. 2023;137(1):59-71. doi:10.1213/ANE.0000000000006467

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CONVENTIONAL BUPRENORPHINE INTIATION APPROACH

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CONVENTIONAL BUPRENORPHINE INTIATION APPROACH

- **Office vs home initiation**
  Buprenorphine induction can be done in the office or at home. Office induction allows for close monitoring.
- **Initial dosing**
  Start with 2-4 mg, can repeat 2 hours later if withdrawal persists. Usual day 1 dose is 8 mg.
- **Prior opioid abstinence**
  Patients should abstain from opioids for at least 12 hours prior to first buprenorphine dose.
- **Managing withdrawal**
  Patients should be in moderate withdrawal before starting buprenorphine.
- **Avoid tobacco**
  Patients should avoid tobacco before dosing due to vasoconstriction effects.

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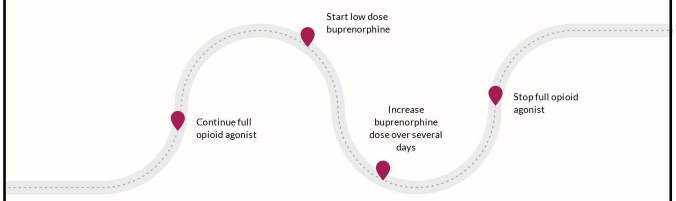
LOW DOSE BUPRENORPHINE INITIATION (LDBI) APPROACH



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WHY LDBI?

1. **Repetitive dosing**
   Repetitive administration of very small buprenorphine doses should not precipitate opioid withdrawal
2. **Drug accumulation**
   Because of the long receptor binding time, buprenorphine will accumulate at the opioid receptor
3. **Replacing full agonist**
   Over time, an increasing amount of the full mu-agonist will be replaced by buprenorphine at the opioid receptor

These hypotheses provide the rationale for using the LDBI approach by slowly transitioning patients from full opioid agonists to buprenorphine without precipitating withdrawal.

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SAMPLE LDBI PROTOCOL

Day	SL Buprenorphine Dose	Full Opioid Agonist Dose
1	0.5 mg once daily	Continue current dose
2	0.5 mg twice daily	Continue current dose
3	1 mg twice daily	Continue current dose
4	2 mg twice daily	Continue current dose
5	4 mg twice daily	Continue current dose
6	8 mg once daily	Continue current dose
7	8 mg QAM and 4 mg QPM	Continue current dose
8	12 mg once daily	Stop

Häxsegl G et al. Subst Abuse Rehabil 2014;7:99–105.
Tecoult D et al. Pharmacother. 2019;39(10):1023–1029.
Bandhana PA et al. CMAJ 2020;192(3):E73.

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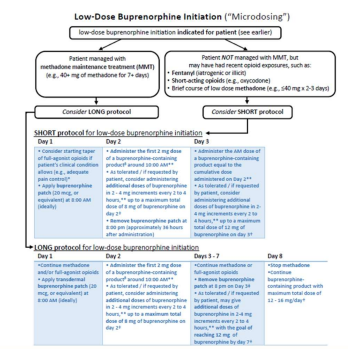
SAMPLE LDBI PROTOCOL



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BUPRENORPHINE INITIATION SUCCESS RATES FOR PATIENTS WITH OUD

Initiation Type	Success Rate
Traditional (n=244)	98.2%
LDBI with SL formulation (n=53)	96.4%
LDBI with TD patch (n=10)	100%
LDBI with IV formulation (n=1)	100%

Spreen LA, Dittmar EN, Quirk KC, et al. Pharmacotherapy. 2022;42(5):411-427. doi:10.1002/phar.2676

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BUPRENORPHINE INITIATION OUTCOMES FOR PATIENTS WITH PAIN

- Traditional initiation for pain patients
  287 patients underwent a 1-7 day traditional initiation with a 92.3% success rate
- LDBI for patients with pain
  29 patients underwent a microdosing initiation with SL buprenorphine, TD patches, or buccal films with a 100% success rate

Spreen LA, Dittmar EN, Quirk KC, et al. *Pharmacotherapy*. 2022;42(5):411-427. doi:10.1002/phar.2676

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BUPRENORPHINE INITIATION OUTCOMES FOR OUD AND PAIN

Traditional initiation for 1 patient Patient given naltrexone then SL buprenorphine, relapsed shortly after	84 LDBIs 100% success rate with SL buprenorphine formulations	9 SL buprenorphine initiations 78% had heroin history, mean OME 369 mg, all completed successfully
73 TD buprenorphine initiations 57% had heroin history, mean OME 230 mg, no relapses reported	2 IV buprenorphine initiations 1 on methadone, 1 illicit opioid use, both completed successfully	

Spreen LA, Dittmar EN, Quirk KC, et al. *Pharmacotherapy*. 2022;42(5):411-427. doi:10.1002/phar.2676

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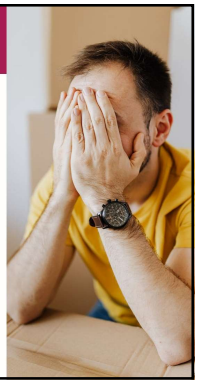
CASE SCENARIO

- John is a 48-year-old male who presents to the outpatient clinic with complaints of chronic back pain due to an injury he sustained five years ago.
- He has a history of taking oxycodone prescribed to manage his pain but admits to taking higher doses than prescribed due to tolerance.
  - Current daily oxycodone dose is 90 mg.
- John expresses a desire to taper off oxycodone but has experienced severe withdrawal symptoms during his previous attempts.
- He is concerned about his increasing dependence on opioids.



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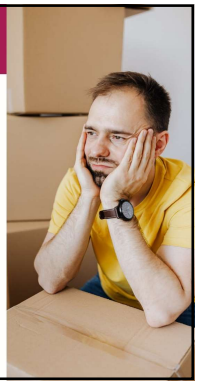
CASE SCENARIO

- John appears anxious and admits to feeling "trapped" by his need for opioids.
- He reports difficulties in his family relationships and job performance due to his opioid use.
- Urine drug testing at today's visit confirms the presence of oxycodone.
- John's health care provider is considering alternative pain management strategies and is concerned about possible opioid use disorder.



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ASSESSMENT QUESTION

Which of the following is a potential next step in the care of this patient?

A. Increasing the dose of oxycodone to address tolerance and withdrawal symptoms.

B. Initiating a slow taper of oxycodone while integrating nonopioid pain management strategies.

C. Initiation of buprenorphine via the conventional approach.

D. Initiation buprenorphine using a low dose protocol.

E. Stopping oxycodone and refer the patient to a methadone clinic.

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OPIOID ANALGESIA IN PATIENTS ON BUPRENORPHINE MAINTENANCE

Dose-dependent increase in mu-opioid receptor occupancy

Experimental study demonstrated dose-dependent increase in mu-opioid receptor occupancy with buprenorphine at 2 mg (41%), 16 mg (85-92%), and 32 mg (94-98%).

Additive or synergistic analgesic effects

Combination of buprenorphine and full mu-opioid receptor agonists has additive or synergistic analgesic effects.

Buprenorphine receptor occupancy does not cause impairment of mu-opioid receptor accessibility.

Recommendations for anticipated vs. emergent pain vary

Protocols that require discontinuation of buprenorphine have negative impact on patient outcomes

Leighton BL et al. Anesth Analg. 2017;125(5):1779-83.
Davis MP et al. Drugs 2018; 78(12): 1251-1220.
Gad A et al. Br J Anaesth 2019; 122(5):e134e142.
Grewal HB et al Neuropsychiatr Dis Treat. 2020;16:2049-2059

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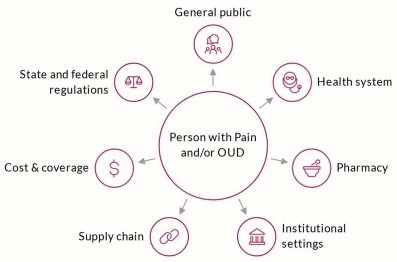
BARRIERS AND FACILITATORS TO BUPRENORPHINE ACCESS



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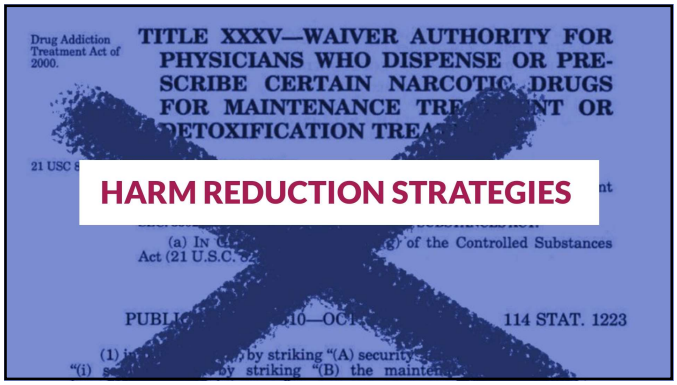

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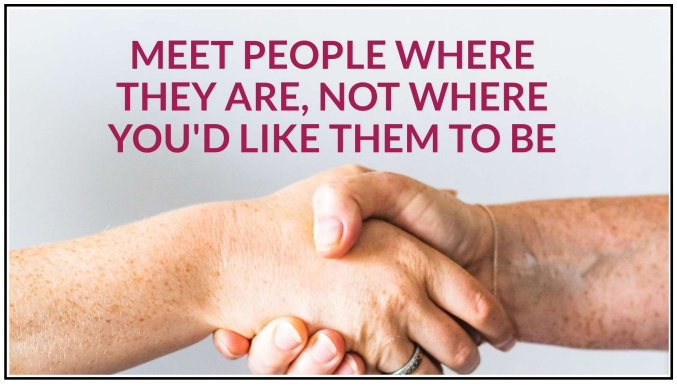

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