Law: Braving Buprenorphine

Exploring Off Label Use of Products for Pain Management and Opioid Use Disorder

December 15th, 2023

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Disclosure

I have no relevant financial relationships with ineligible companies or conflicts of interest to disclose.

This presentation will discuss off label uses of buprenorphine products.

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Objectives

1. Review the unique pharmacology of buprenorphine (BUP) including opioid receptor activity and binding affinity

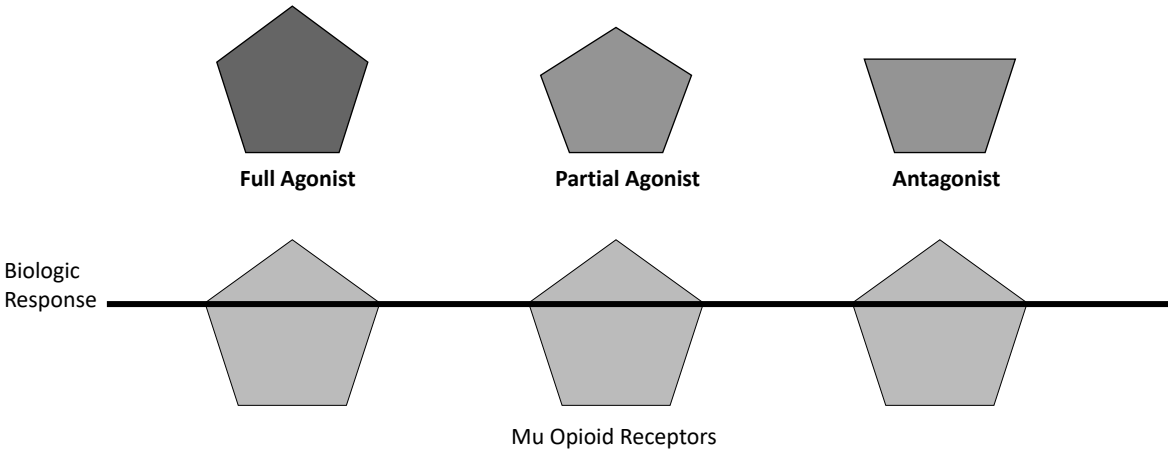
2. Differentiate between the FDA approved buprenorphine products and their indications

3. Identify a comprehensive plan for safe and efficacious use of buprenorphine products for pain and opioid use disorder (OUD)

4. Recognize the utility of prescribing off label use of buprenorphine products and legislature that supports such practice

3

BUP Pharmacology



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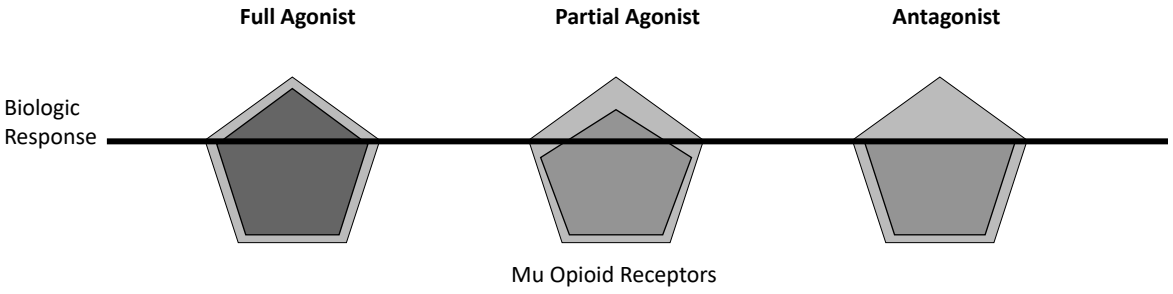

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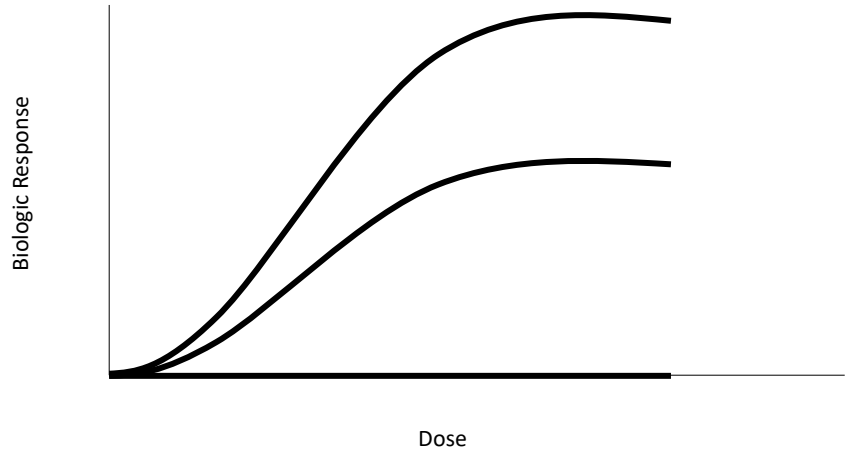
5

Partial vs. Full Opioid Agonist



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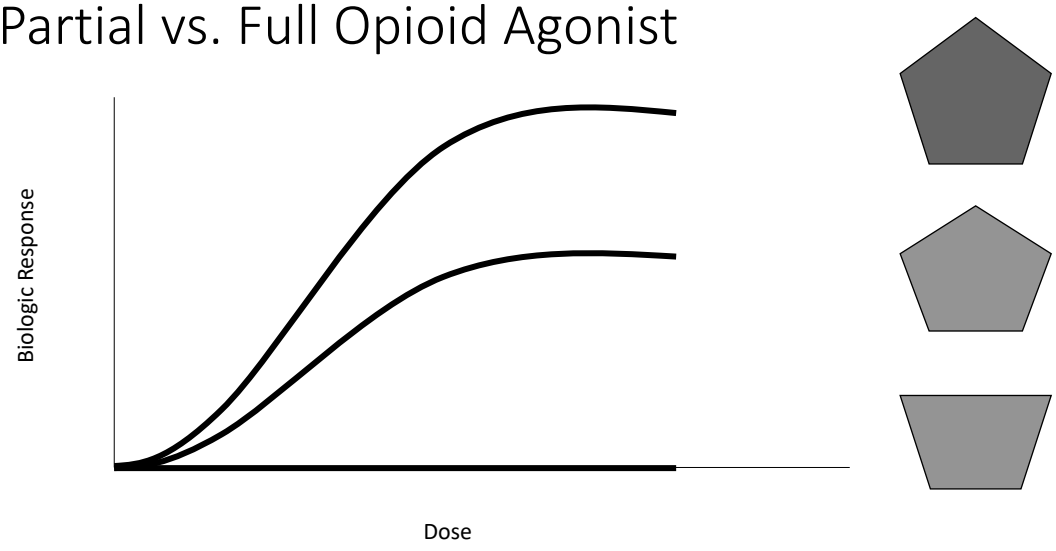

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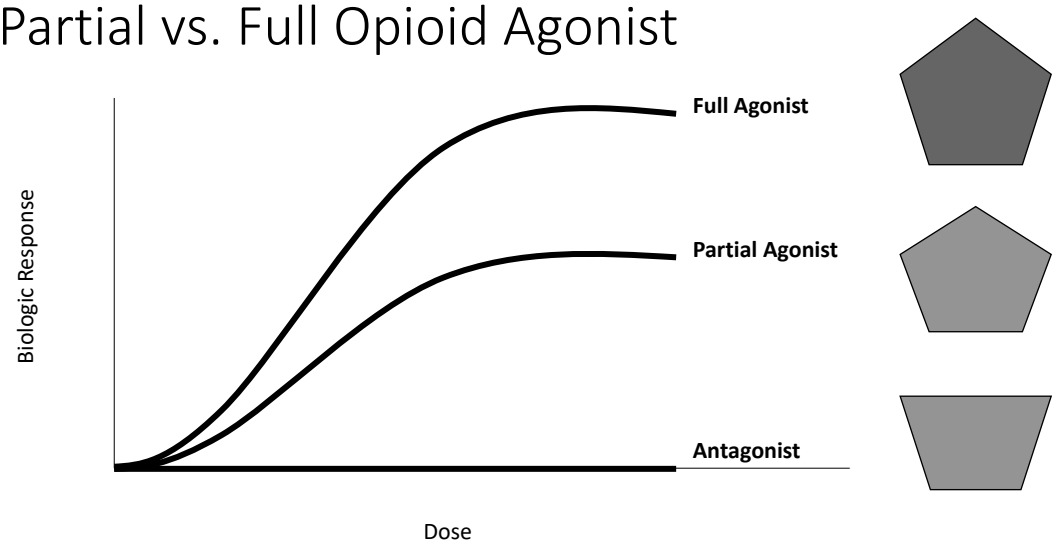

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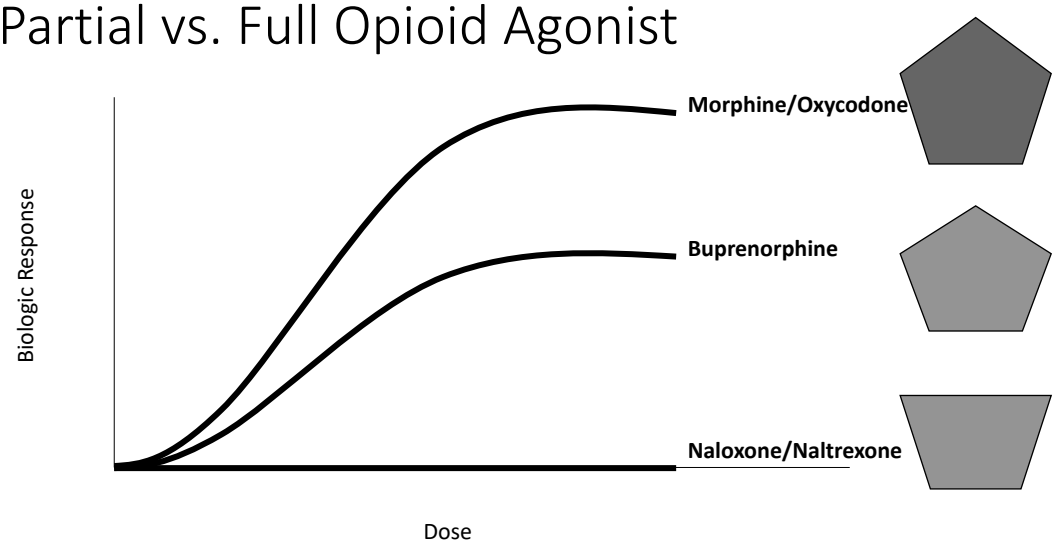

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Opioid Receptor Effects of BUP

Receptor	Mu	Kappa	Delta	ORL1
Activity	Partial Agonist	Antagonist vs. Inverse Agonist?	Antagonist	Agonist
Binding Affinity	High	High	High	Low

Proposed to have a higher impact on spinal opioid receptors compared to brain receptors

Gudin J, Fudin J. Pain Ther (2020) 9:41–54.
Heit HA, Gourlay DL. Clin J Pain. 2008 Feb; 24(2): 93-97.
Vanderah TW. Clin J Pain. 2010; 26: S10-S15.

10

BUP at the Mu-Opioid Receptor (MOR)

Buprenorphine Dose	MOR Occupancy	Clinical Effects at MOR Occupancy
< 1 mg	<15%	**Analgesia at 5-10%**
1 mg	15-29%	
2 mg	28-47%	
4 mg	45-64%	**Withdrawal suppression at 50%**
8 mg	65-80%	
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24 mg	85-96%	
32 mg	88-98%	

Greenwald MK, Comer SD, Fiellin DA. Drug Alcohol Depend. 2014 November; 0: 1–11.

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BUP Formulations and Indications

FDA Approved for Pain

(dosing in mcg)

Belbuca® (buccal film)

Butrans ® (transdermal patch)

Buprenex ® (injection solution)

FDA Approved for OUD

(dosing in mg)

Suboxone® (sublingual film)

Subutex® (sublingual tablet)

Sublocade® (subcutaneous injection)

Bunavail® (buccal film)

Zubsolv® (sublingual tablet)

Brixadi® (subcutaneous injection)

Probuphine® (subdermal implant)

Poliwoda S et al. Health Psychol Res. 2022; 10(3): 37517.
Substance Abuse and Mental Health Services Administration. Medications for Opioid Use Disorder For Healthcare and Addiction Professionals, Policymakers, Patients, and Families. Updated 2020.

12

Audience Question #1

Which of the following is a pharmacologic mechanism of BUP?

A. Antagonist at the delta opioid receptor
B. Antagonist/inverse agonist at the kappa opioid receptor
C. Partial agonist at the mu opioid receptor
D. Agonist at the ORL1 opioid receptor
E. All of the above are pharmacologic mechanisms of BUP

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Legislative Changes for Prescribing Buprenorphine as a Medication for OUD (MOUD)

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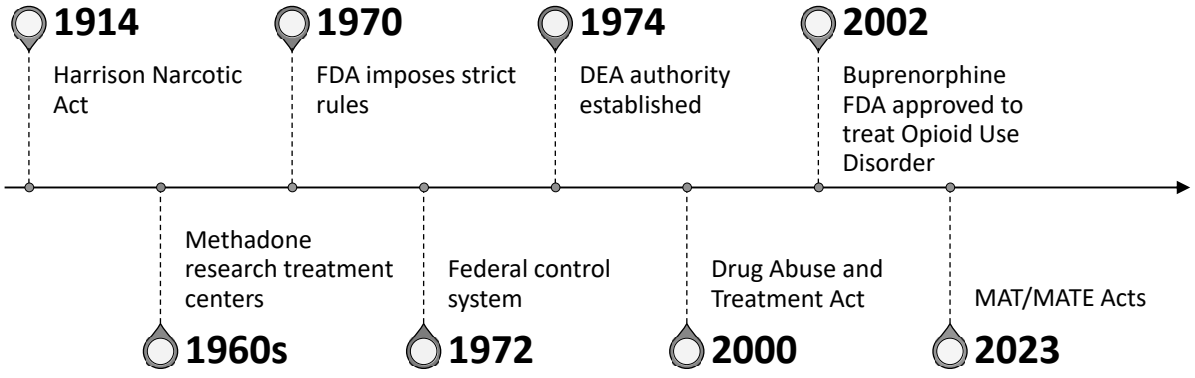
Timeline of OUD Policy in the U.S.



Annu Rev Public Health. 2018;39:525-541.
Int J Drug Policy. 2019;74:257-265.

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Treatment of OUD

Addiction: primary, chronic disease of brain reward, motivation, memory and related circuitry

Stigmatizing assumption: medications like methadone and buprenorphine don't work; they're just a substitute for non-prescribed opioids

Scientific understanding: MOUD stabilizes brain chemistry, blocks the euphoric effects of opioids, relieves physiological cravings, and improves physical and mental health

NIDA. Drugs, Brain, and Behavior: The Science of Addiction.
Larochelle MR, et al. Ann Intern Med. 2018;169:137-145.
Liebschutz JM, et al. JAMA Intern Med. 2014;174(8):1369-1376.

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MAT Act S.445

- **MAT: Mainstreaming Addiction Treatment**
  - **Removes** the requirement that a health care practitioner apply for a separate waiver (also referred to as an X-waiver) through the Drug Enforcement Administration (DEA) to dispense buprenorphine for MOUD
  - Substance Abuse and Mental Health Services Administration (SAMHSA) will conduct a national campaign to educate health care practitioners and encourage them to integrate substance use disorder treatment into their practices

https://www.congress.gov/bill/117th-congress/senate-bill/445

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MAT Act S.445

- **MAT: Mainstreaming Addiction Treatment**
  - All practitioners who have a current DEA registration that includes Schedule III authority, may now prescribe buprenorphine for opioid use disorder in their practice if permitted by applicable state law.
  - There are no longer any patient caps. A practitioner may treat as many patients as they can support with buprenorphine.

https://www.congress.gov/bill/117th-congress/senate-bill/445

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MATE Act S.2235

- **MATE: Medication Access and Training Expansion**
  - Requires health care providers, as a condition of receiving or renewing a registration to prescribe potentially addictive drugs, to complete **a one-time training** on managing patients with substance use disorders
  - Department of Health and Human Services must award grants to health professional associations and education programs for integrating substance use disorder training into relevant curricula.
  - **Effective as of June 27, 2023**

https://www.congress.gov/bill/117th-congress/senate-bill/2235?q=%7B%22search%22%3A%5B%22Medication+Access+and+Training+Expansion%22%5D%7D&r=2&s=10

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Implications of These Law Changes

- Increased access to evidence-based treatment for OUD
- Decreased mortality related to OUD
- Increased clinician education
- Decrease healthcare costs
- Perceived decreases in stigma and bias

Ashford RD, et al. Drug Alcohol Depend. 2018;189:131-138.
FitzGerald C, Hurst S. BMC Med Ethics. 2017;18(1):19.
Shatterproof Addiction Stigma Index. 2021. Accessed 11/10/23.

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Impact of MOUD

- MOUD ↓ **all-cause and overdose-related mortality**, illicit opioid use, disease rates, and criminal legal involvement
- Hospital or ED-initiated buprenorphine is associated with ↓ **rates of other opioid use** and ↑ **engagement in treatment** after discharge compared to discharge without MOUD

- MOUD also associated with decreased morbidity:
  - Improved social functioning
  - Decreased injection drug use
  - Reduced risk of HIV/HCV infection

Sordo L, et al. BMJ. 2017;357:j1550.
Larochelle MR, et al. Ann Intern Med. 2018;169:137-145.
Liebschutz JM, et al. JAMA Intern Med. 2014;174(8):1369-1376.

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Pharmacotherapy Mortality Reduction Across Common Chronic Disease States

OUD	• Patients on active MOUD→ **82%** less likely to die of an overdose and ↓ all-cause mortality by **~50%**
Hypertension	• ACE Inhibitors reduce the risk of all-cause mortality by **13%** and cardiovascular deaths by **17%**
Asthma	• Regular use of inhaled steroids reduces risk of death by **60%**
Diabetes	• SGLT-2i and GLP-1a's reduce mortality risk by **27%** and **25%**, respectively

Addiction. 2020;115(8):1496-1508
SAMHSA MAT Effectiveness. Updated 7/25/2022. Available at:https://www.samhsa.gov/medication-assisted-treatment
Thorax 2002;57:683-686
Sordo L, et al. BMJ. 2017;357:j1550.
JAMA Intern Med. 2014;174(5):773–785
BMJ Open Diabetes Research and Care 2020;8:e000940

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Stigma and Bias

- Substance Use Disorders (SUD) including OUD are the most stigmatized conditions in the U.S. and worldwide
- 75% of the public doesn't believe SUD is a medical illness
- 50% believe addiction is caused by bad character/lack of moral strength
- **Healthcare providers have similar levels of stigma**
  - Are legislative changes + education enough?
  - How do we continue to address clinician stigma and bias?

    Addictionary®. Recovery Research Institute.

    Words Matter - Terms to Use and Avoid When Talking About Addiction. 2021.

Ashford RD, et al. Drug Alcohol Depend. 2018;189:131-138.
FitzGerald C, Hurst S. BMC Med Ethics. 2017;18(1):19.
Shatterproof Addiction Stigma Index. 2021. https://www.shatterproof.org/our-work/ending-addiction-stigma/shatterproof-addiction-stigma-Index. Accessed 11/15/23.

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Audience Question #2

Which of the following statements is **false**?

A. The MATE act requires health care providers who prescribe controlled substances to complete annual competency training for managing patients with OUD
B. MOUD decreases all cause mortality by 50% in patients with OUD
C. The passing of the MAT act increases patient access to evidence-based treatment of OUD
D. Patients with OUD experience higher rates of stigma and bias both from the public and from health care providers

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Audience Question #2

Which of the following statements is **false**?

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Low Dose Initiation of Buprenorphine for MOUD

"Micro-Dosing" ; Using products FDA approved for pain

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BUP at the Mu-Opioid Receptor (MOR)

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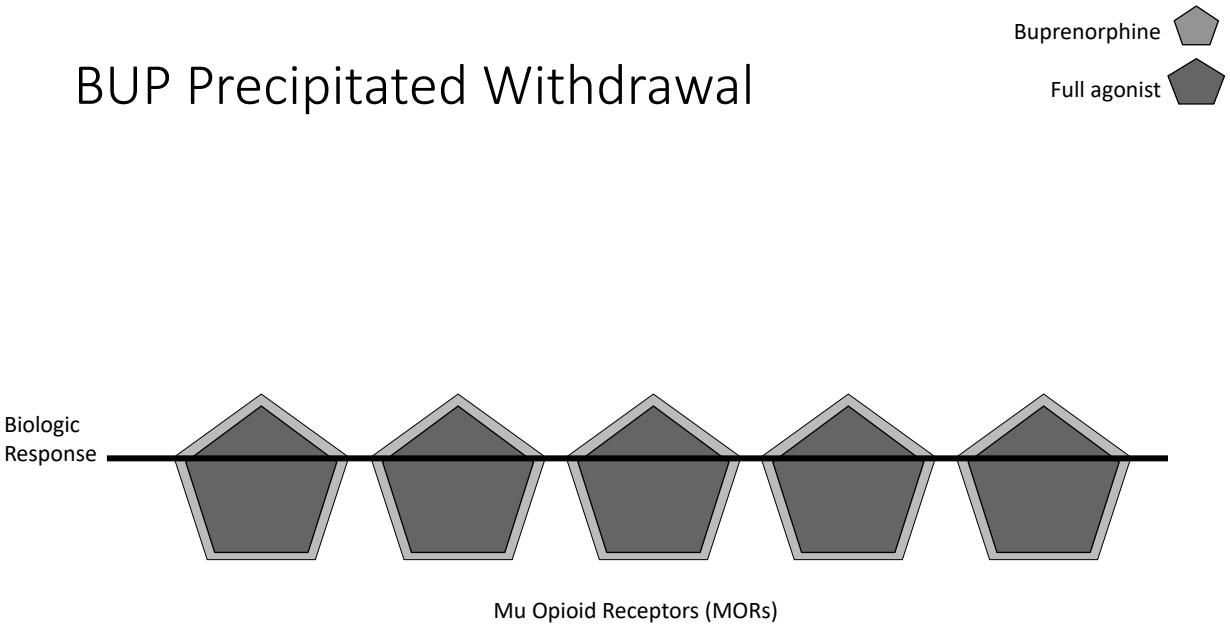
MOR Binding Affinity

Binding Affinity	Drug	Ki (nM)
Higher ↕ **Lower**	Buprenorphine	0.22
	Hydromorphone	0.37
	Oxymorphone	0.41
	Morphine	1.17
	Fentanyl	1.35
	Methadone	3.38
	Oxycodone	25.87
	Hydrocodone	41.58
	Codeine	734.2
	Tramadol	12,486

Volpe DA, et al. Regul Toxicol Pharmacol. 2011 Apr; 59(3): 385–390

30

BUP Precipitated Withdrawal



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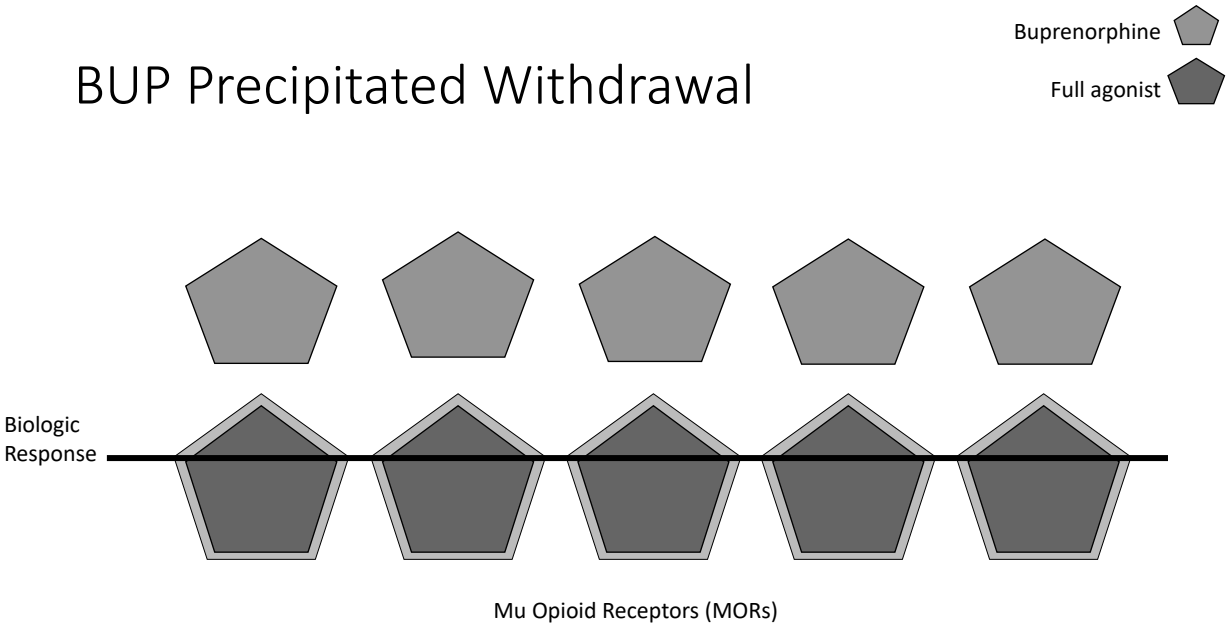

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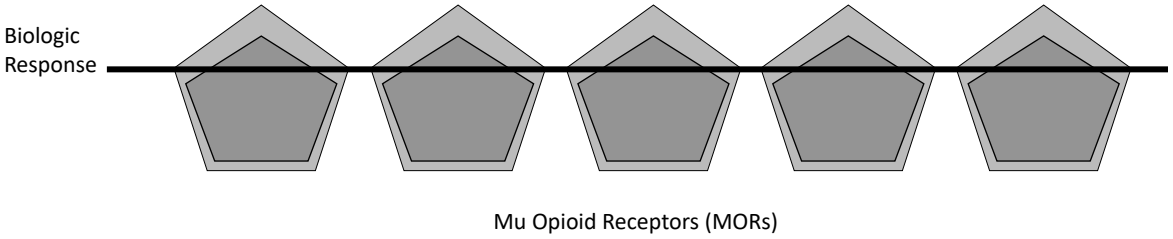
BUP Precipitated Withdrawal

Buprenorphine

Full agonist



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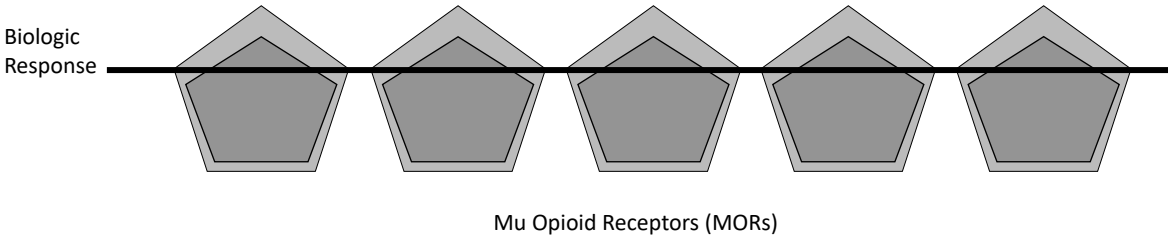
BUP Precipitated Withdrawal

Buprenorphine

Full agonist

Precipitated Withdrawal: rapid and intense onset of withdrawal symptoms caused by medications that block or reverse the effects of full agonist opioids

Symptoms are MORE severe and intense than natural, gradual, withdrawal



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Standard Initiation vs. Low Dose Initiation

Standard initiation

Stop all full opioid agonists, wait for the emergence of mild/moderate withdrawal symptoms to occur, then can initiate first dose of BUP

Low dose initiation

Does not require a period of opioid abstinence and the emergence of withdrawal symptoms

- Severe, uncontrolled pain
- Long term opioid use and tolerance +/- hyperalgesia
- Intolerable opioid withdrawal symptoms

Quirk K, Stevenson M. J Palliat Med. 2022 Jan; 25(1): 145-154.

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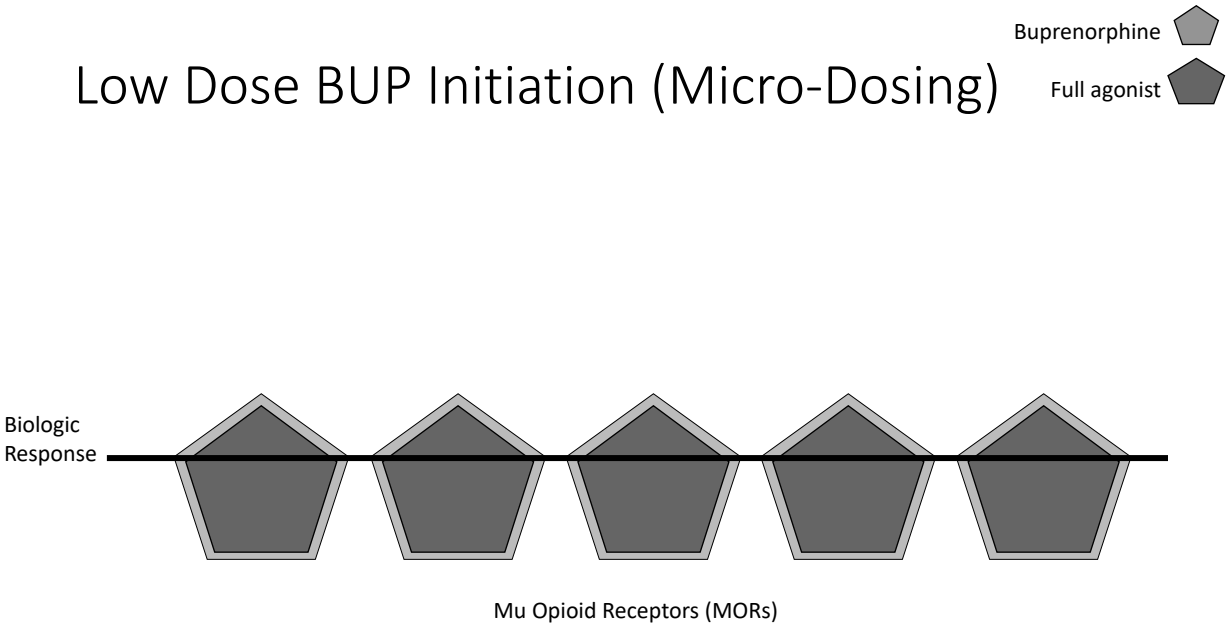
Low Dose BUP Initiation (Micro-Dosing)



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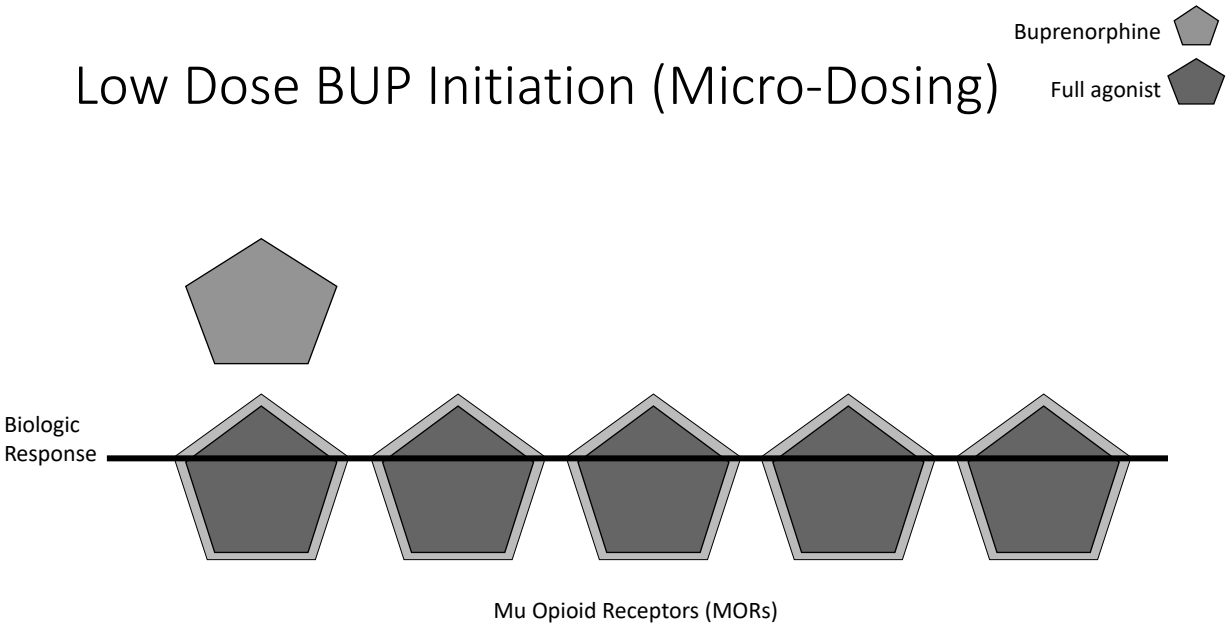

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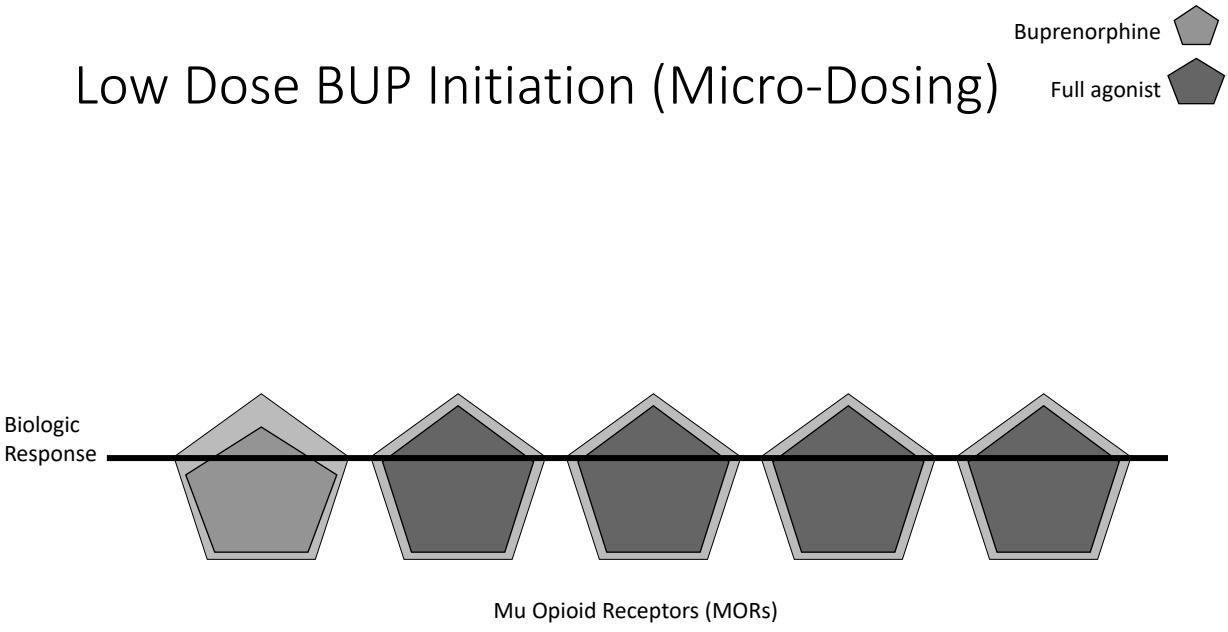

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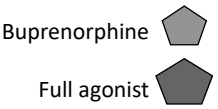

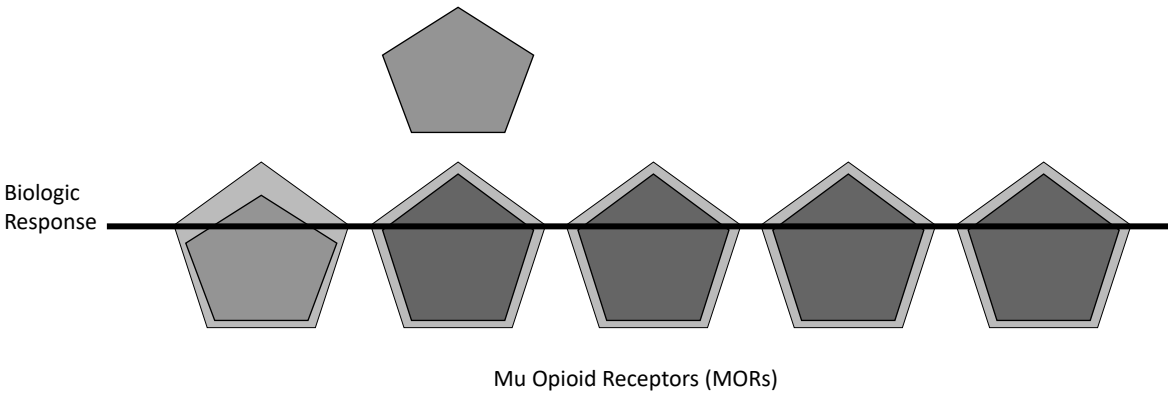

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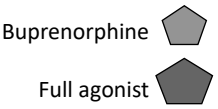

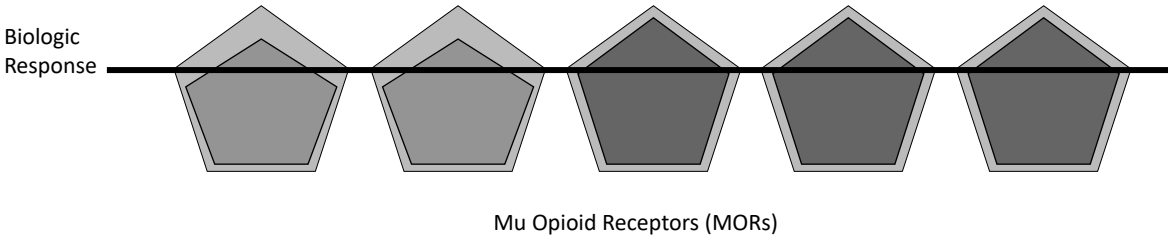

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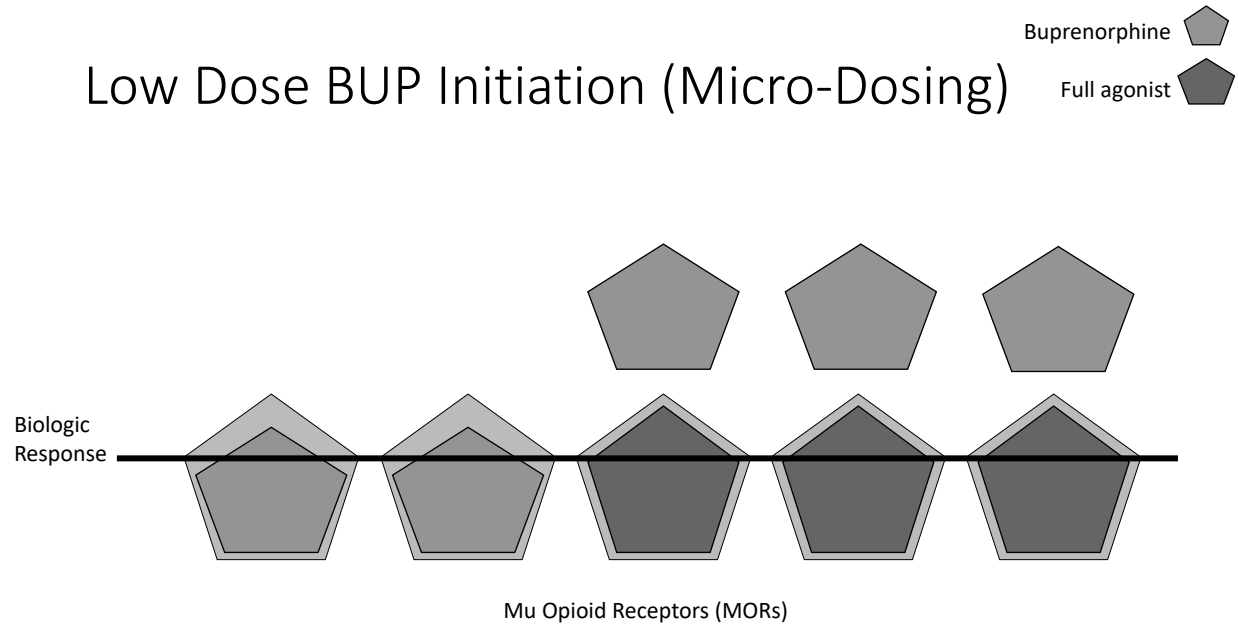

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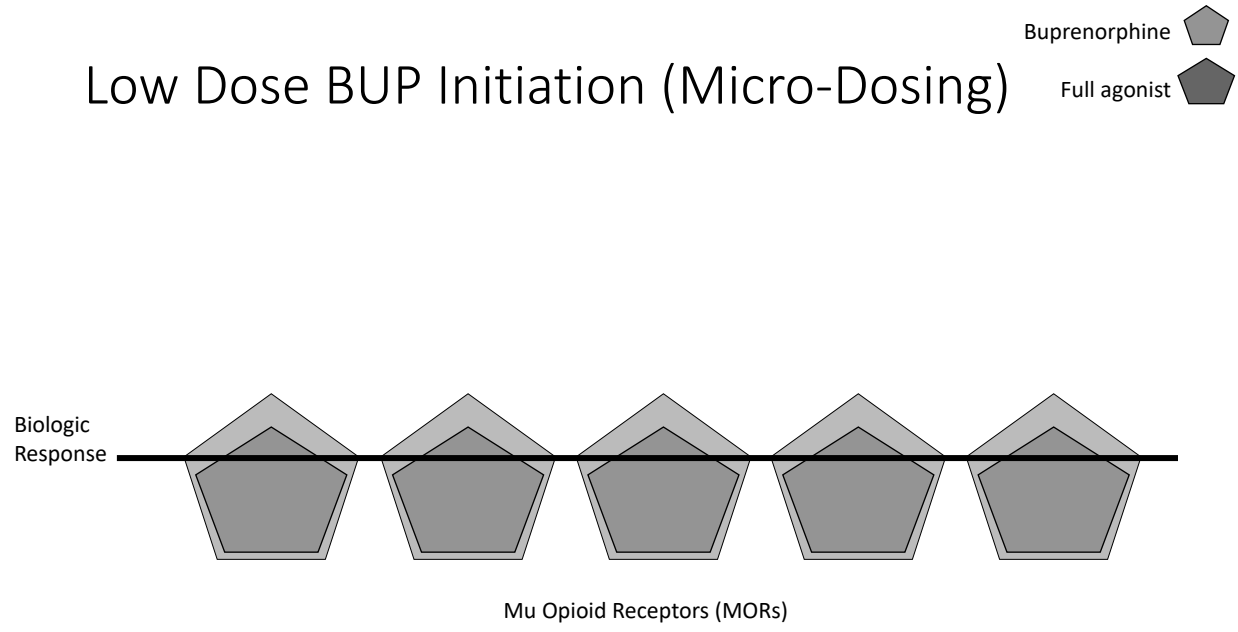

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Low Dose Initiation Strategies

- 2022 review of 34 low dose BUP initiation publications
  - RCTs, observational studies, retrospective reviews and case reports/series
- Variety of BUP products used
  - 24 studies used SL tabs/films FDA approved for OUD
  - 10 studies used BUC films or TD patches FDA approved for pain
- **Starting doses ≤ 1 mg SL (or equivalent)** are generally safe and effective **and unlikely to cause precipitated withdrawal**
  - Precipitated withdrawal symptoms were rare; measured using COWS
- Duration of low dose initiation varied from 3-23 days

Randomized controlled trials (RCTs), sublingual (SL), buccal (BUC), transdermal (TD), Clinical opioid withdrawal scale (COWS)

Quirk K, Stevenson M. J Palliat Med. 2022 Jan; 25(1): 145-154.

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Low Dose Initiation with OUD Products

- Goal of starting doses ≤ 1 mg SL BUP or equivalent
  - Lowest available dose commercially available → 2 mg SL
- Split dosing of SL BUP products not approved by FDA/TJC
  - Utilized outpatient in some cases
  - Limitations in acute care setting
- Barriers/limitations
  - Patient health literacy
  - Adherence
  - Dexterity
  - Complexity of instructions

U.S. Food and Drug Administration (FDA), The Joint Commission (TJC)

Quirk K, Stevenson M. J Palliat Med. 2022 Jan; 25(1): 145-154.
Reindel KL, DeAngelis MJ, Ferrara AS, et al. Int J Pharm Compd 2019;23:258–263.

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Low Dose Initiation with Pain Products

IV BUP	Buccal BUP	Transdermal BUP
0.3 mg/ml vials (1 ml)	**75, 150, 300, 450, 600**, 750, 900 mcg film	**5, 10, 15, 20** mcg/hr patch

- Allow for low dose initiation/titration ***without*** product manipulation
- Do **NOT** require tapering of full agonist first
- Can be accomplished in variety of care settings
  - Barrier → cost/insurance coverage

Quirk K, Stevenson M. J Palliat Med. 2022 Jan; 25(1): 145-154.

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Comparing BUP Products

Bioavailability of BUP products

IV BUP	Buccal BUP	Transdermal BUP	Sublingual BUP
100%	46-65%	15%	29% ± 10%

Approximate **equivalent dosing** of BUP products

IV BUP	Buccal BUP	Transdermal BUP	Sublingual BUP
0.3 mg	600 mcg (max dose 1,800 mcg/day)	4 x 20 mcg/hr (max dose 20mcg/hr)	1 mg

Poliwoda S et al. Health Psychol Res. 2022; 10(3): 37517.

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Low Dose Initiation Protocol Example

Day	Buccal Buprenorphine (Belbuca) Film Dose	Sublingual Buprenorphine/Naloxone (Suboxone) Film Dose	Full Opioid Agonist Dosing
Day 1	Belbucca 150 mcg BUC BID	---	Full dose
Day 2	Belbucca 300 mcg BUC BID	---	Full dose
Day 3	Belbucca 600 mcg BUC BID	---	Full dose
Day 4	---	Suboxone 2 mg SL BID	Full dose
Day 5	---	Suboxone 4mg SL BID	Full dose
Day 6	---	Suboxone 8 mg SL daily	Full dose – last day
Day 7	---	Suboxone 12 mg SL daily	---
Day 8	---	Consider additional adjustments based on clinical presentation; may increase to 24 mg daily.	---

BID – twice daily, BUC – buccal, SL – sublingual

Adult Guideline for Micro-Dosing Buprenorphine for Management of OUD in Patients Receiving Full Agonist Opioids. UK HealthCare Guideline. Updated 2/8/2022

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Rapid Low Dose Initiation Protocol Example

Day	Buccal Buprenorphine (Belbuca) Film Dose	Sublingual Buprenorphine/Naloxone (Suboxone) Film Dose	Total dose of BUP/day	Full Opioid Agonist Dosing*
Day 1	Belbucca 300 mcg BUC x 1 THEN (4 hrs later) 600 mcg BUC Q4H **x 5 doses**	---	**3.3 mg**	Full dose
Day 2	---	2 mg SL Q6H **x 4 doses**	**8 mg**	Full dose –last day
Day 3	---	4 mg SL Q3H **x 2 doses** **THEN** **8 mg x 1**	**16 mg max**	---
Day 4	---	Consider additional adjustments based on clinical presentation	**Up to 24 mg max daily dose**	---

BID – twice daily, BUC – buccal, SL – sublingual

Adult Guideline for Micro-Dosing Buprenorphine for Management of OUD in Patients Receiving Full Agonist Opioids. UK HealthCare Guideline. Updated 2/8/2022

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Audience Question #3

- Sue B. Ocksone is a 32 yo female with hx of chronic pain following a MVC 6 years ago. She was originally prescribed oxycodone for pain by her PCP. Her use of oxycodone increased despite her injuries resolving. When her PCP stopped prescribing oxycodone, she turned to buying it illicitly as she was unable to function without it and experienced significant withdrawal when she ran out.
- After 2 years of increasing oxycodone use, decreasing function and stealing from friends and family to continue to self-medicate, she was diagnosed with OUD. She states that she is interested in starting MOUD with buprenorphine.
- She tells you she has been using oxycodone that she buys off the street. She denies using heroin/fentanyl. She reports no history of injection drug use.
- She tells you that on average she is using oxycodone 80 mg 4-5 times per day (approx. 400-500 OME)

Hx (history), MVC (motor vehicle crash), PCP (primary care provider)

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Audience Question #3

Based on the literature review, which of the following *starting doses* is **LEAST** appropriate for low dose initiation of buprenorphine in the setting of full agonist opioid use?

A. IV Buprenorphine 0.6 mg
B. Buccal Buprenorphine 150 mcg
C. IV Buprenorphine 0.15 mg
D. Buccal buprenorphine 300 mcg
E. All of the above are safe initial doses for low dose initiation

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Chronic Pain Management with Buprenorphine

Using products FDA approved for OUD

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BUP as an Option for Chronic Pain

- Unique pharmacologic properties
- Comparable analgesic efficacy to full opioid agonists
- Increased efficacy for mixed/neuropathic pain conditions
- Less development of tolerance
- Lower risk of opioid induced hyperalgesia
- Safe for use in patients with renal/hepatic impairment
- CIII vs. CII

Dowell D et al. Patient-Centered Reduction or Discontinuation of Long-term Opioid Analgesics: The HHS Guide for Clinicians. JAMA. 2019 Nov 19;322(19):1855-1856. doi: 10.1001/jama.2019.16409.

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BUP as an Option for Chronic Pain

- Unique pharmacologic properties
- Comparable analgesic efficacy to full opioid agonists
- Increased efficacy for mixed/neuropathic pain conditions

Department of Health & Human Services (HHS)

Recommends BUP as an alternative pain management option for those patients **"on high opioid dosages and are unable to taper despite worsening pain and/or functioning with opioids, whether or not OUD criteria are met"**

Dowell D et al. Patient-Centered Reduction or Discontinuation of Long-term Opioid Analgesics: The HHS Guide for Clinicians. JAMA. 2019 Nov 19;322(19):1855-1856. doi: 10.1001/jama.2019.16409.

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Enhanced Safety and Tolerability Compared to Full Agonist Opioids

Lower incidence of opioid related adverse effects with BUP

- Lower risk of respiratory depression
- Little/no immunosuppressive effects
- Less opioid-indued constipation
- Little/no euphoria
- Safe in renal/hepatic impairment

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Limitations of Products Approved for Pain

- Recommended max doses

IV BUP	Buccal BUP Film*	Transdermal BUP Patch*
Max dose: 0.6 mg	Max dose: 900 mcg BID	Max dose: 20 mcg/hr

- IV use limited to acute pain/acute care settings
- Reported prolongation of QTc informed max dosing*
- Higher needs – cancer pain, opioid tolerant, end-of-life
- Cost/insurance coverage

*SL buprenorphine products dosed at significantly higher total daily doses have **NOT** been associated with prolongation of QTc interval

BUPRENEX (buprenorphine solution for injection) [Prescribing information]. North Chesterfield, VA. Indivior, Inc. Oct 2019.
BELBUCA (buprenorphine buccal film) [Prescribing Information]. Stoughton, MA: Collegium Pharmaceutical, Inc.; June 2022.
BUTRANS (buprenorphine transdermal patch, extended-release) [Prescribing Information]. Stamford, CT: Purdue Pharma; June 2022.

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Products Approved for OUD

- No target doses and increased dosing frequency for pain
- BUP mono products vs. BUP/NAL combo product
- Increased stigma and bias associated with these products
- State specific prescribing restrictions may apply

SL BUP	SubQ BUP	Subdermal BUP implant
Suboxone®* Subutex® Zubsolv®*	Sublocade® Brixadi®	Probuphine®

Buprenorphine/naloxone combo product (BUP/NAL)*

Substance Abuse and Mental Health Services Administration. Medications for Opioid Use Disorder For Healthcare and Addiction Professionals, Policymakers, Patients, and Families. Updated 2020.

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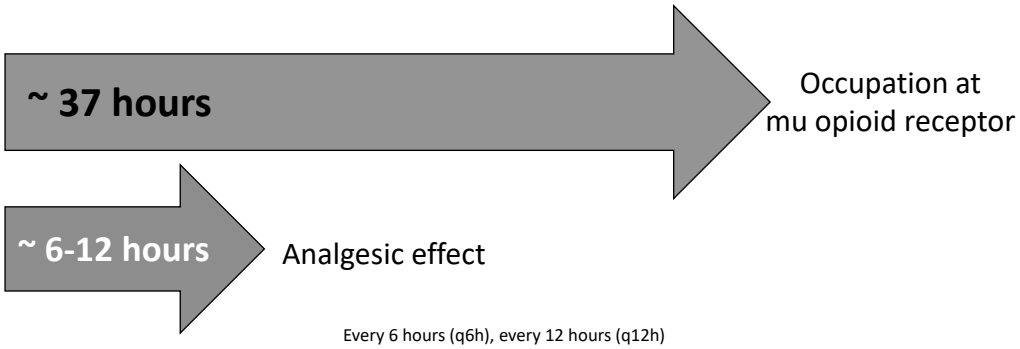
Target Doses and Dosing Frequency

- Once daily dosing of BUP for MOUD
- **Increased dosing frequency of BUP for pain**
  - Dosing 2-4 times per day (q6h – q12h) will improve analgesic efficacy



Every 6 hours (q6h), every 12 hours (q12h)

Childers J et al. J Palliat Med 2012;15(5):613-614
Johnson R et al. J Pain Symptom Manage 2005; 29(3):297-326

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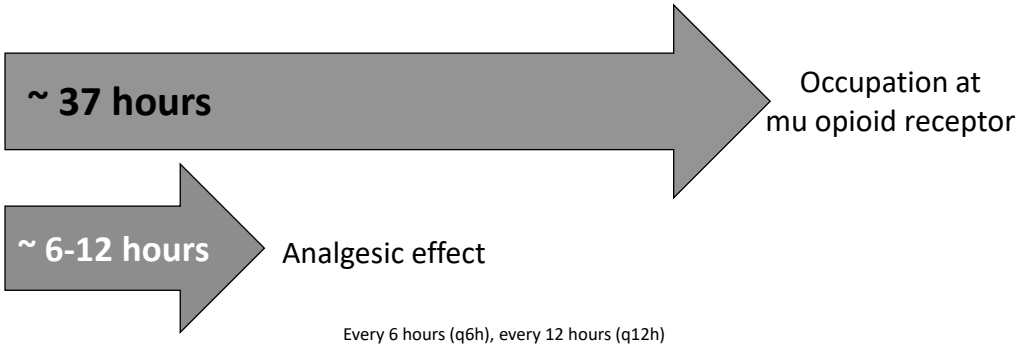
Target Doses and Dosing Frequency

What is the **target dose** of BUP for chronic pain management?

- Once daily dosing of BUP for MOUD
- **Increased dosing frequency of BUP for pain**
  - Dosing 2-4 times per day (q6h – q12h) will improve analgesic efficacy



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Johnson R et al. J Pain Symptom Manage 2005; 29(3):297-326

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BUP vs. BUP/NAL

What is the utility of BUP/NAL?

- Abuse deterrent for dosage form manipulation; parenteral use
- If injected NAL bioavailability ↑ can induce precipitated withdrawal

Is SL BUP equivalent to SL BUP/NAL for analgesia?

- Insignificant differences in bioavailability, tolerability and efficacy

Is BUP/NAL 'better' than BUP mono?

- Not associated with improved health outcomes

Yan Chen K etl al. Anesthesiology May 2014, Vol. 120, 1262–1274.
Kelty E, et al. J Psychopharmacol. 2018 Mar;32(3):344-352. Epub 2018 Feb 13.

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Efficacy for Analgesia

Article	Daitch J, et al. Pain Phys. 2012;15(suppl 3):ES59-ES66.	Malinoff HL, et al. Am J Ther 2005;12(5):379-84.
Study Type	Retrospective study (n=104) chronic pain patients rotated off full agonist opioids to SL BUP/NAL (OME 10-840; mean OME 180 mg/day)	Open label study (n=95) chronic pain patients rotated to SL BUP or BUP/NAL (mean BUP doses = 8 mg/day divided)
Conclusions	Statistically significant reduction (-2.3; P<0.001) in reported pain scores (0-10 NRS) for patients previously on morphine, oxycodone, or fentanyl	86% (82/95) demonstrated substantial improvement in pain scores, improvements in mood, sleep disturbance, and well-being

Oral morphine equivalence (OME), numeric rating scale (NRS)

Daitch J, et al. Pain Phys. 2012;15(suppl 3): ES59-ES66.
Malinoff HL, et al. Am J Ther 2005;12(5):379– 84.
Cote J, Montgomery L.. Pain Med. 2014;15(7):1171-1178. doi:10.1111/pme.12 386.

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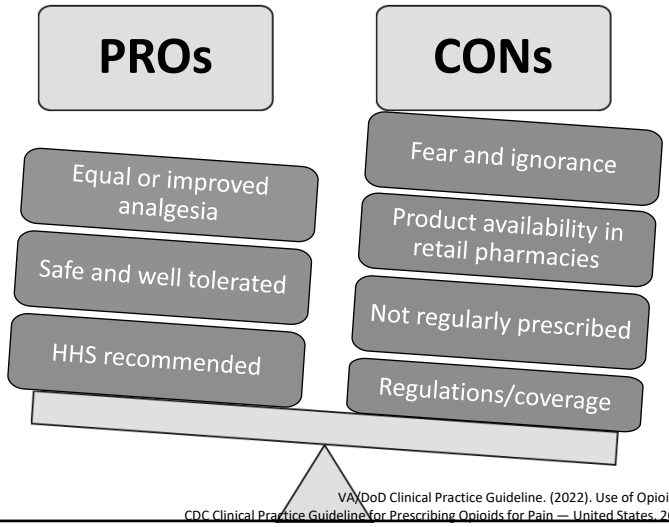
Stigma and Bias Impact on Utility of BUP for Pain Management



VA/DoD Clinical Practice Guideline. (2022). Use of Opioids in the Management of Chronic Pain Work Group
CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95

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Audience Question #4

When utilizing BUP for the treatment of chronic pain, clinicians should aim for what target dose?

A. 20 mcg/hr TD patch Q7days
B. 450-900 mcg buccal BID
C. 2 mg SL Q6H
D. 8 mg SL BID
E. There is no target dose for chronic pain

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Audience Question #4

When utilizing BUP for the treatment of chronic pain, clinicians should aim for what target dose?

A. 20 mcg/hr TD patch Q7days
B. 450-900 mcg buccal BID
C. 2 mg SL Q6H
D. 8 mg SL BID
E. There is no target dose for chronic pain

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Key Take Home Points

- BUP is a pharmacologically unique medication with data to support its utility as a safe and effective treatment of pain **and** OUD
- BUP products can be safely and successfully used off label for low dose initiation of MOUD and for chronic pain
- Legislative changes have lifted the federal prescribing requirements for prescribing BUP for treatment of OUD
- Stigma and bias continue to be major pervasive factors in access to high quality care for patients with OUD and chronic pain

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Law: Braving Buprenorphine

Exploring Off Label Use of Products for Pain Management and Opioid Use Disorder

December 15th, 2023

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