Update on Chronic Pain Management in OUD: Utilizing Buprenorphine

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1 October 2021

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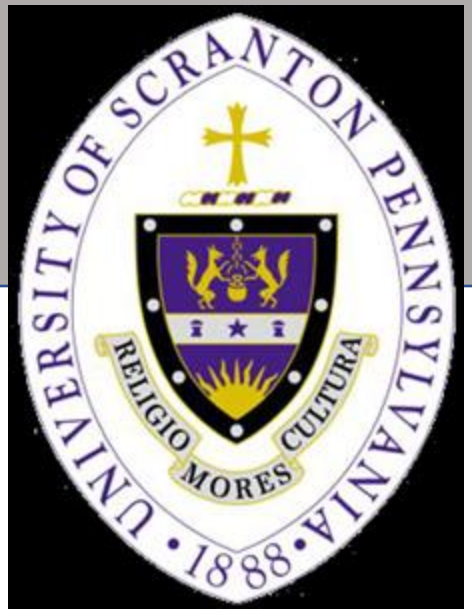
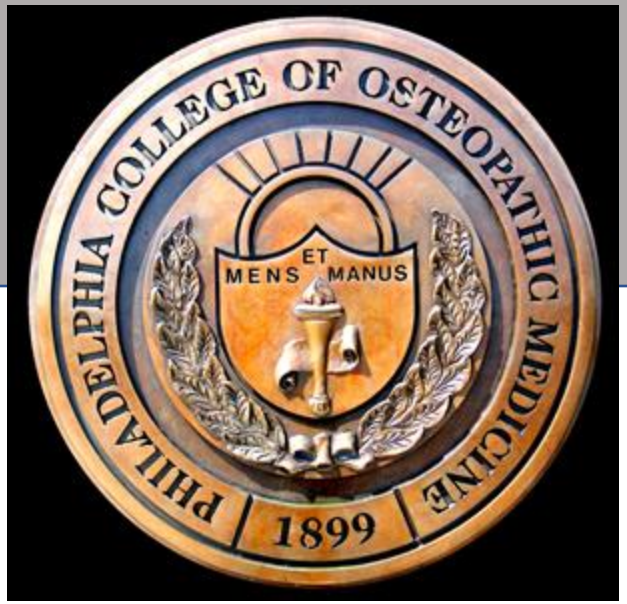
Disclosures

We have no disclosures to report

- Dr. James Bailey – No disclosures
- Dr. Clement Chen – No disclosures





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Objectives

- To compare and contrast the characteristics of full and partial mu-receptor agonists

- To understand how to address chronic pain in the OUD population
- To describe buprenorphine's mechanism of action for analgesia and the two forms of buprenorphine available to treat chronic pain
- To understand how to utilize buprenorphine in the treatment of chronic pain and perioperative pain in the substance use disorder population
- To describe compliance measures utilized for the management of patients on chronic opioid therapy and medication-assisted treatment

Assessing Pain in Patients with OUD

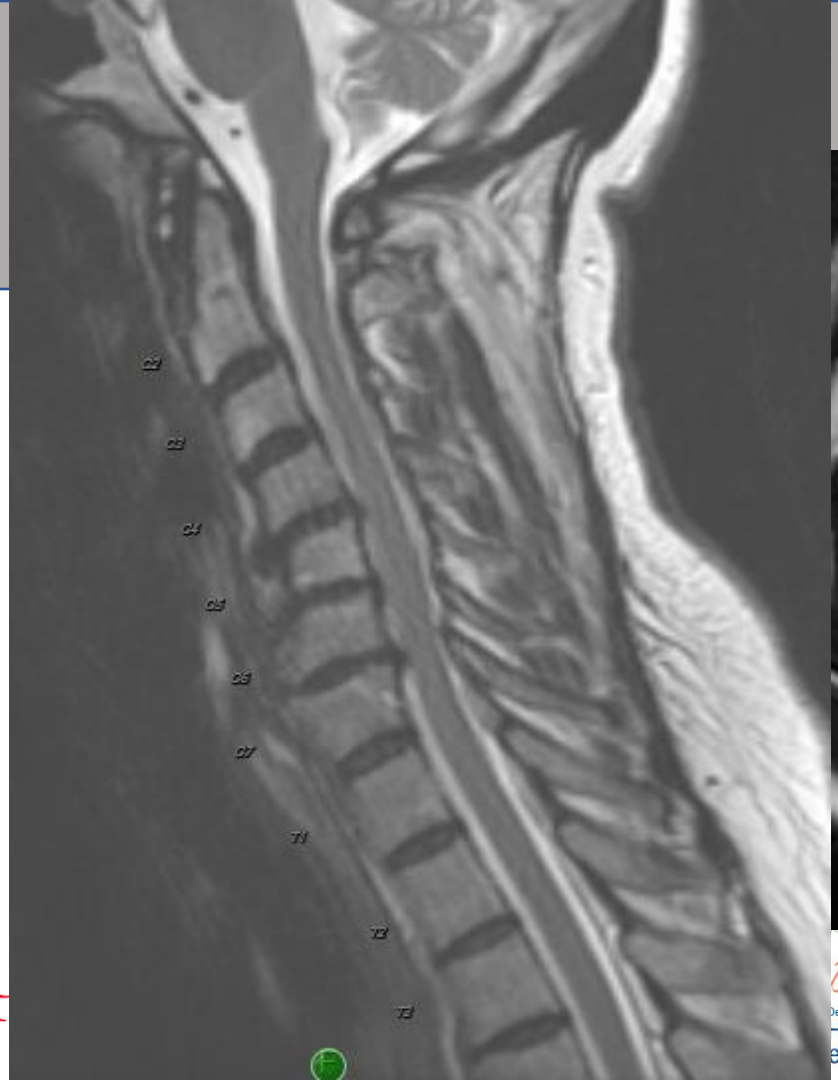
- Inquire about the reason for opiate use?
  - Recreational? Self-treatment for mood disorder? Self treatment for pain?
- Perform a thorough physical examination and workup of the pain complaint in addition to addressing OUD/SUD
  - Take advantage of the captive audience
- Treat the cause of the pain in the setting of OUD

Treating Pain in Patients with OUD

- Osteopathic Manipulative Treatment
- Physical Therapy
- Utilize adjunctive analgesics
  - Neuroleptics: pregabalin, gabapentin
  - Muscle relaxants: baclofen, tizanidine
  - SNRIs: duloxetine, milnacipran
- Injections
  - Peripheral joints, bursae, spinal
- Mental Health Services

Case Example

- 56F presenting for MAT evaluation who was self-medicating with oxycodone and amphetamine for severe radiating neck pain.
- Florid hyperreflexia on physical examination. Gait ataxia.
- Work-up revealed severe central stenosis from C4-7. Underwent ACDF C4-7.
- Stable on buprenorphine/naloxone 4mg/1mg three times daily
- Anesthesia: high dose hydromorphone and ketamine drip
- Post-op: Hold buprenorphine. Oxycodone 10mg or 15mg.
- Restarted buprenorphine/naloxone 4mg/1mg three times daily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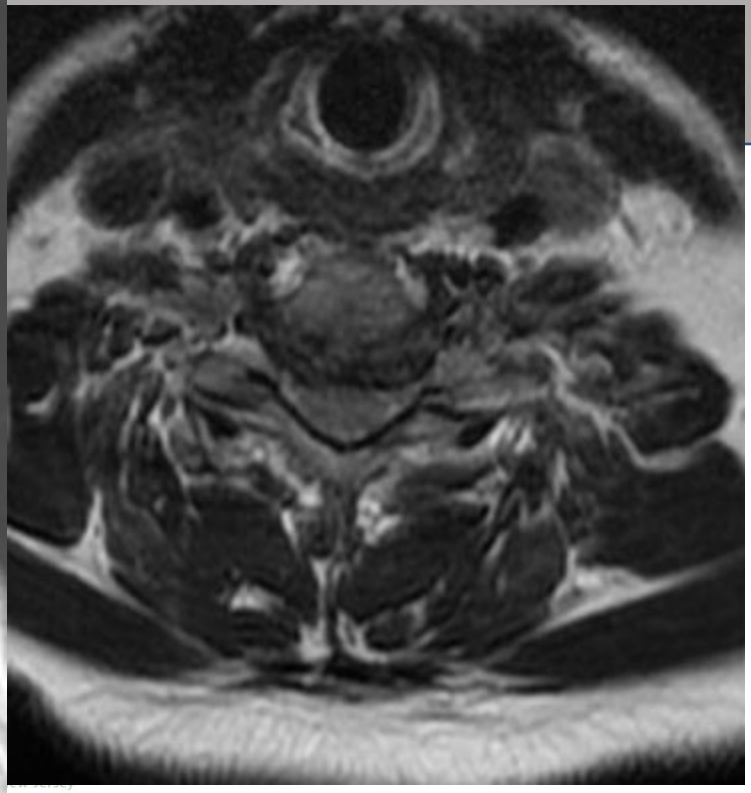


Chronic Pain Epidemiology

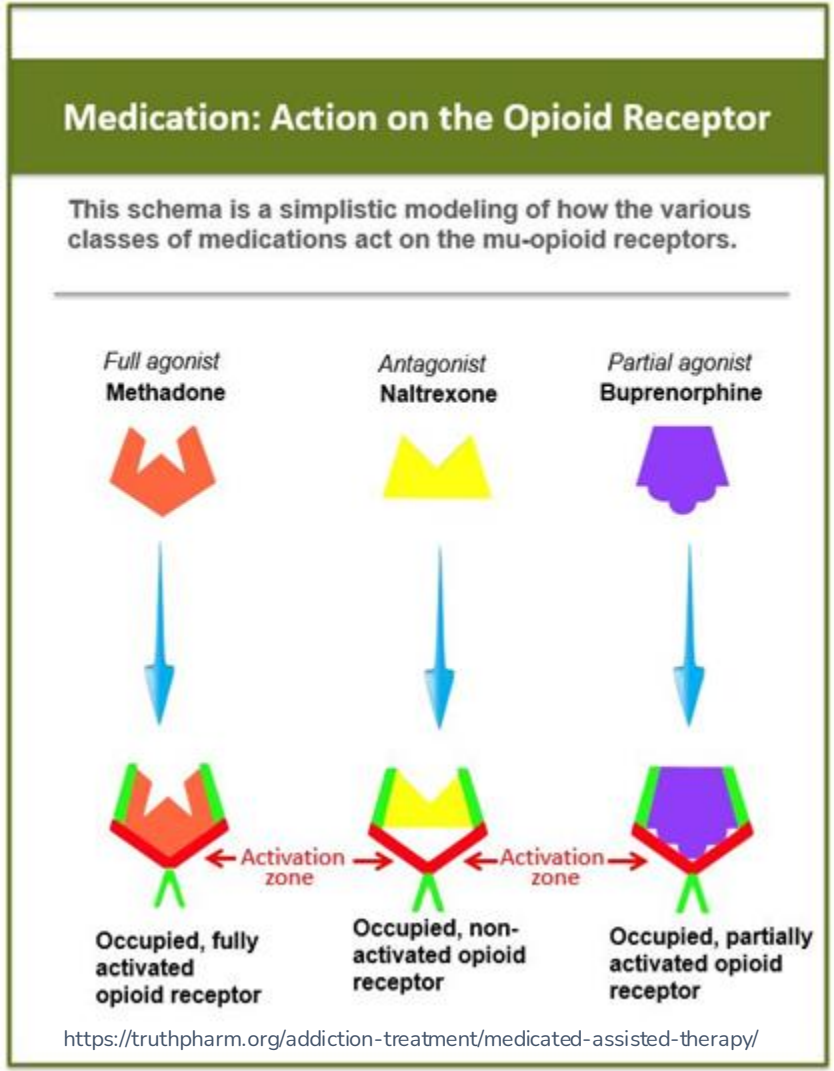
- Affects 100 million adults (more than heart disease, diabetes, and cancer combined)[5]
- Cost $600 billion annually[5]
- 215 million Rx in US in 2016
- >90 MME Rxs trending downward (2006-2016 reduced by 46.8%)
- BUT overdose deaths 5 higher in 2016 vs 1999
- Narcan Rx is now required by law in NJ
- Max 5 day Rx for new patients

Full mu-Receptor Agonists

- Codeine (Tylenol #3)
- Morphine (MSIR, MS Contin)
- Hydrocodone (Vicodin/Vicoprofen)
- Hydromorphone (Dilaudid/Exalgo)
- Oxycodone (Percocet/Endocet/Oxycontin/Xtampza))
- Oxymorphone (Opana)
- Fentanyl (Duragesic)
- Methadone
- Tramadol (Ultram IR/ER)
- Tapentadol (Nucynta IR/ER)

Partial mu-receptor agonist- Buprenorphine

- Semisynthetic opioid created in 1966[1]
- Derivative of thebaine
  - Intermediate in production of oxycodone, buprenorphine
- FDA approved use for Opioid Use Disorder 2002
- Frequently misunderstood!



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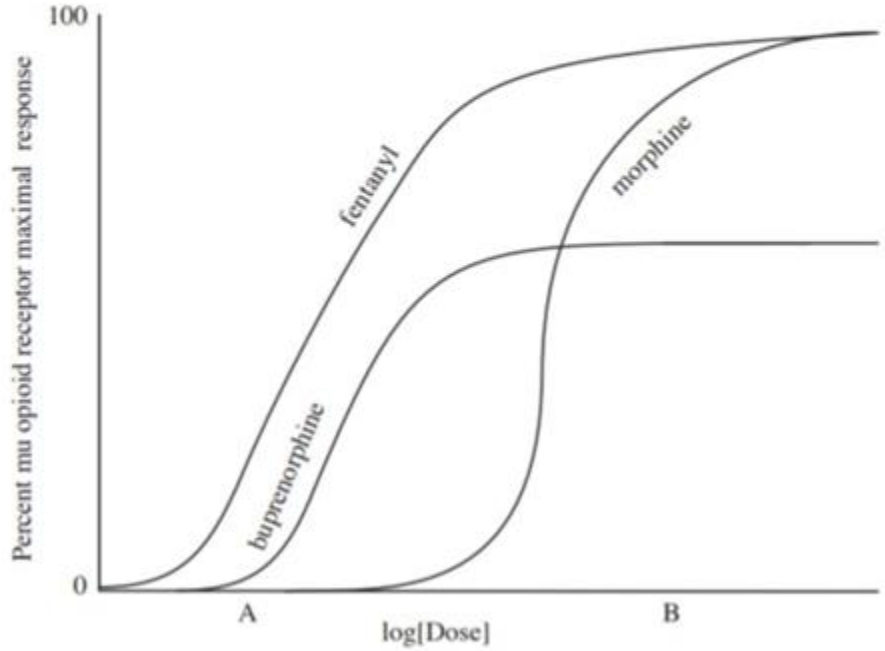
PMC full text:
J Addict Med. Author manuscript; available in PMC 2020 Aug 21.
Published in final edited form as:
J Addict Med. 2019 Mar-Apr; 13(2): 93–103.
doi: 10.1097/ADM.0000000000000457

Figure 1.



Dose-response curve schematic of three opioid agonists. At a low dose (Dose A), fentanyl and buprenorphine produce significantly greater responses than morphine (i.e., fentanyl and buprenorphine are more potent than morphine). While fentanyl response is dose-related until reaching 100% maximal response, buprenorphine effects reach a ceiling, at which point further increases in dose do not increase the magnitude of response. Because buprenorphine is a partial agonist, it cannot not produce a 100% response like a full agonist (i.e., fentanyl) can. At higher doses (Dose B), morphine (a full agonist with low potency) produces greater response

Buprenorphine

- **Ceiling effect for respiratory depression but not for analgesia**[1]
- Partial mu-receptor agonist at **spinal cord level**
  - Key for limiting respiratory depression
- Does not affect brainstem

- Does not have reinforcing effects from nucleus accumbens, prefrontal cortex, and ventral tegmental area.[1]

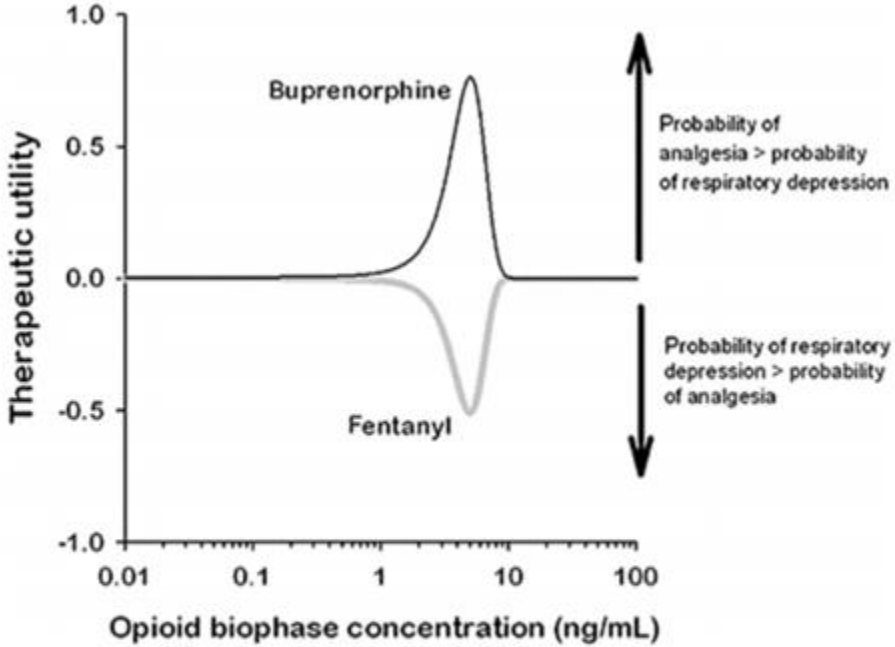


Fig. 1. Relative therapeutic utility of buprenorphine and fentanyl. (*Modified from* Yassen A, Olofsen E, Kan J, et al. Pharmacokinetic-pharmacodynamic modeling of the effectiveness and safety of buprenorphine and fentanyl in rats. Pharm Res. 2008; 25(1): 183-193; with permission.)

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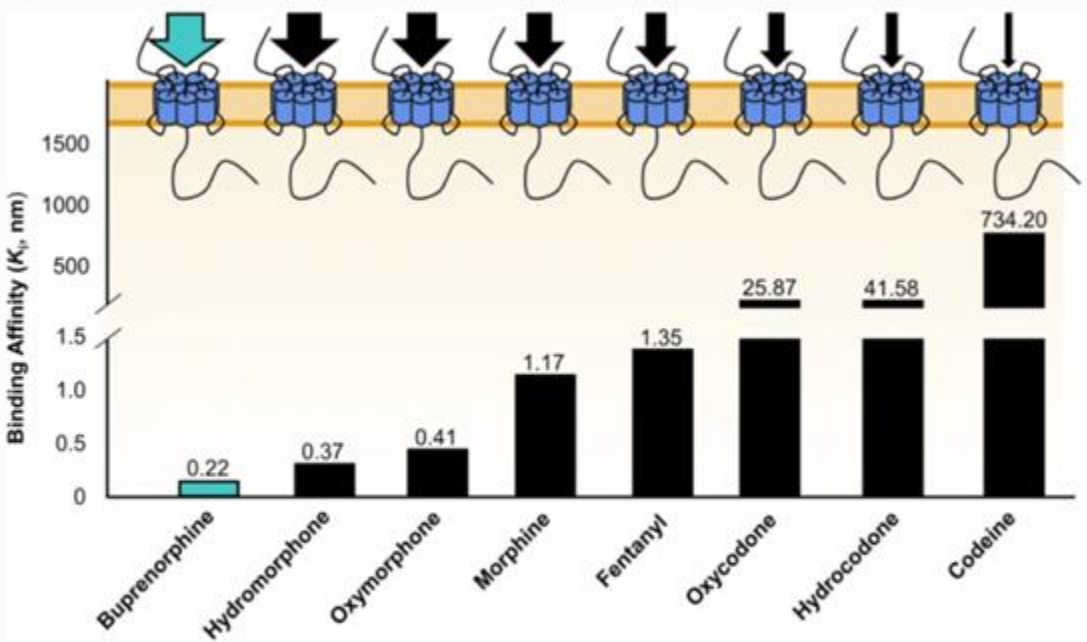
Buprenorphine: High affinity[4]

- 1.7 times > hydromorphone
- 5.4 times > morphine
- 6.2 times > fentanyl
- 120 times > oxycodone

- High dose fentanyl can surmount buprenorphine blockade
- Narcan (naloxone) 4mg can also surmount blockade

Fig. 1



Buprenorphine exhibits a higher binding affinity at the μ-opioid receptor than full μ-opioid receptor agonists. A low K_i value corresponds to greater binding affinity but does not necessarily translate to greater receptor activity [48]

https://link.springer.com/article/10.1007/s40122-019-00143-6

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Buprenorphine: High potency[4]

- CANNOT be converted to morphine milliequivalents
- Does not pose overdose risk like full mu-agonists like doses >90 MME

- CDC does not have conversion table for buprenorphine

Buprenorphine: Slow Dissociation from mu[4]

- Long duration of action
- High dose buprenorphine attenuates response to full mu-agonists up to 98 hours after last dose

Buprenorphine: Pharmacokinetics[4]

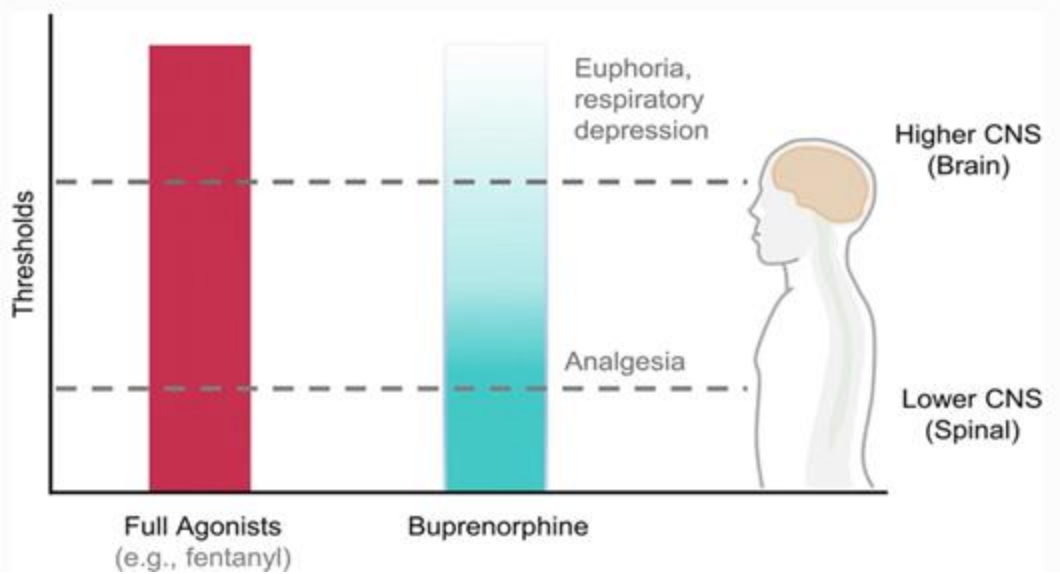
- High bioavailability after IV/SC administration
- Low bioavailability after SL/buccal administration
- 50% for buccal, 15% transdermal
- Half life: 24-42 hours

- Metabolism: SL/buccal via first pass to **norbuprenorphine** via CYP450 3A4/5
- Should see metabolite in urine
- Elimination 10-30% urine and remainder through stool
  - Excellent for patients with renal and hepatic disease.

Buprenorphine and analgesia

- 25/75-100x more potent than morphine[1,2]
- Scarce evidence of overdose but can be reversed with naloxone 4mg[1,4]
- Anti-hyperalgesic effect
  - As opposed to full mu-agonists

- Voltage-gated Na^+ channel activity that can affect **neuropathic pain**[1]
- DM peripheral neuropathy example.



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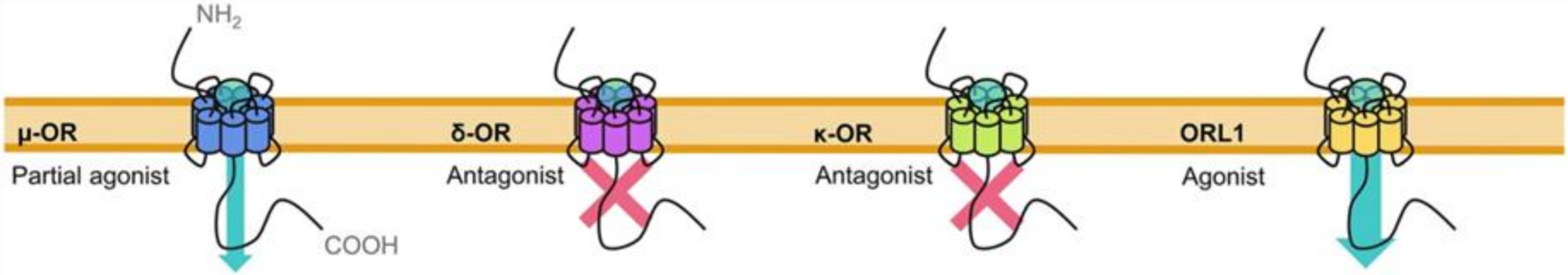
Buprenorphine and Kappa receptor

- Opioid **agonists** of kappa receptor → dynorphin production → hyperalgesia and antinociceptive tolerance.
- Example: Patients on high doses of opioids reporting increased pain.

- Buprenorphine **antagonizes** kappa receptor
  - Inhibits negative reinforcement loop and emotional states produced by opioid withdrawal



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

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

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

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

Buprenorphine Side Effects

- Nausea
- Dizziness
- Less constipation
- Little to no immunosuppression compared to full mu-agonists[1]
- Less likely to affect gonadal axis and decrease testosterone[1]
- QT_c prolongation of 9.2ms in 40 µg/hr transdermal patch
  - 20-60ms is clinically significant

Buprenorphine Initiation for Chronic Pain

- Taper to less than 30 MME
- Use adjunctive agents to augment pain during that time
  - Neuroleptic agents (gabapentin, pregabalin)
  - SNRIs (duloxetine, milnacipran)
  - Muscle relaxants (baclofen, tizanidine)
  - NSAIDs
  - Osteopathic Manipulative Treatment
  - Physical Therapy

Buprenorphine Clinical Pearls

- Use as long-acting agent for chronic pain management
- Can be used with short-acting opiates for breakthrough pain
- Peak concentration at 60 hours
- Steady state at 72 hours→ point at which dose can be changed
- Prescriptions can be refilled

Buprenorphine Products Examples and Dosages

https://butrans.com/patient/what-is-butrans.html

- Buccal- Belbuca®

https://www.belbuca.com/starting-treatment

- Sublingual

https://www.zubsolv.com/zubsolv/patient-preferred/

With naloxone to deter IV abuse

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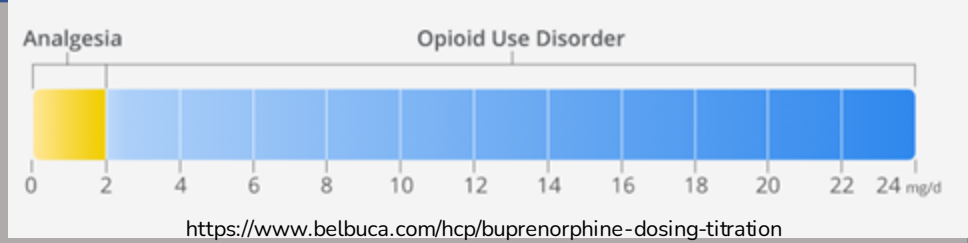
Buccal Buprenorphine



https://www.belbuca.com/hcp/buprenorphine-dosing-titration

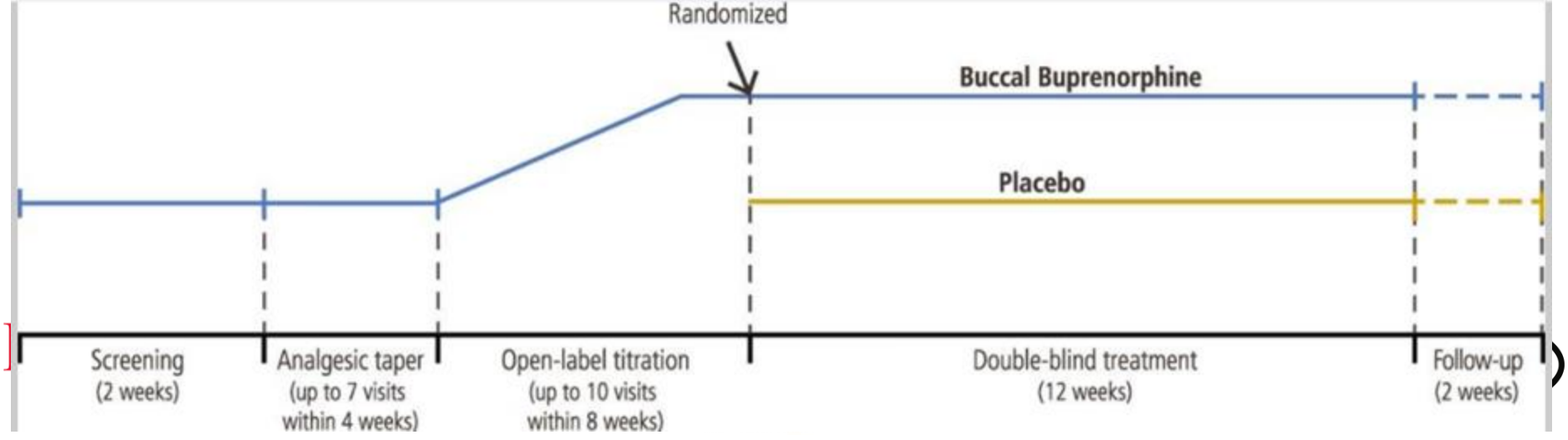
After tapering their current opioid down to 30 mg/d oral MME or less[1]

Step 1	Step 2	Step 3					
FIND Previous daily dose (prior to taper)	DETERMINE BELBUCA STARTING DOSE	Titrate BELBUCA to Optimal Dose*					
		1	2	3	4	5	6
<30 mg oral MME	75 mcg† once daily or q12h	150 mcg	300 mcg	450 mcg	600 mcg	750 mcg	900 mcg
30–89 mg oral MME	150 mcg q12h	300 mcg	450 mcg	600 mcg	750 mcg	900 mcg	
90–160 mg oral MME	300 mcg q12h	450 mcg	600 mcg	750 mcg	900 mcg		

For patients previously taking oral MME >160 mg, consider an alternative analgesic.

Efficacy and tolerability of buccal buprenorphine in opioid-experienced patients with moderate to severe chronic low back pain: results of a phase 3, enriched enrollment, randomized withdrawal study[7]

- Patients 30-160 MME
- n = 254 placebo
- n = 257 buprenorphine
- Tapered to <30 MME, allowed 2 rescue doses of BTP medications
- Buprenorphine titrated then randomized into placebo or buprenorphine groups



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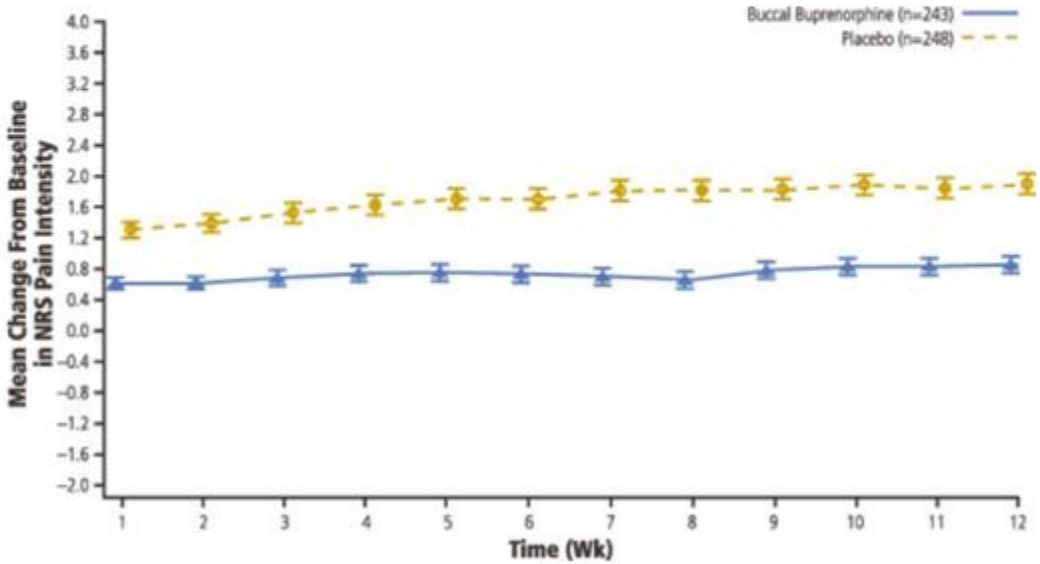
PAIN

PMC full text:

Pain. 2016 Nov; 157(11): 2517–2526.

Published online 2016 Jul 18. doi: 10.1097/j.pain.0000000000000670

Figure 3.



Mean (SE) change from baseline in NRS pain intensity in double-blind treatment period (with imputed values). NRS, numerical rating scale.

PMC full text:

Pain. 2016 Nov; 157(11): 2517–2526.

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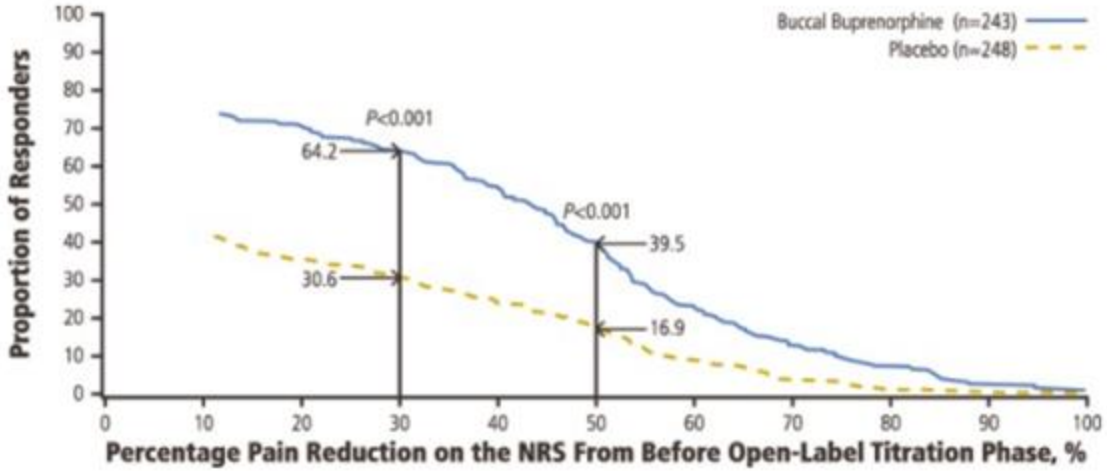
Figure 5.



Proportion of responders with selected percentage pain reduction before open-label titration to week 12 in the double-blind treatment period.

Efficacy and tolerability of buccal buprenorphine in opioid-experienced patients with moderate to severe chronic low back pain: results of a phase 3, enriched enrollment, randomized withdrawal study[7]

- Transdermal buprenorphine (Butrans) effective in patients <80 MME/day
- Buccal buprenorphine (Belbuca) effective in patients < 160 MME/day

Perioperative Pain Management: A Paucity of Evidence[3]

- Level 5: Continue preoperative dosage
- Level 5: Adjunctive analgesics (NSAIDs, acetaminophen, gabapentin/pregabalin, lidocaine, ketamine)
- Level 4: Initiate full mu-agonist(fentanyl, hydromorphone, morphine), or decrease buprenorphine dose to decrease receptor blockade
- Level 5: D/C planning with buprenorphine and possibly full mu-agonist if needed. Risk/benefit with OUD
- Level 5: Engage outpatient buprenorphine prescriber to assist with perioperative pain management

COMPLIANCE MEASURES

- Peer review groups to unify patient approach for challenging cases
- Reviewing PMP at every visit
- Urine drug screens every 3 months (NJ Law requires annual)
  - Both Rapid, if necessary, and confirmatory
- Pill counts and urine drug screens if there is aberrant results or behaviors
- Warning letters
- Limiting quantity of medications prescribed
  - Medicare guidelines: 90 days max
- Behavioral health referral

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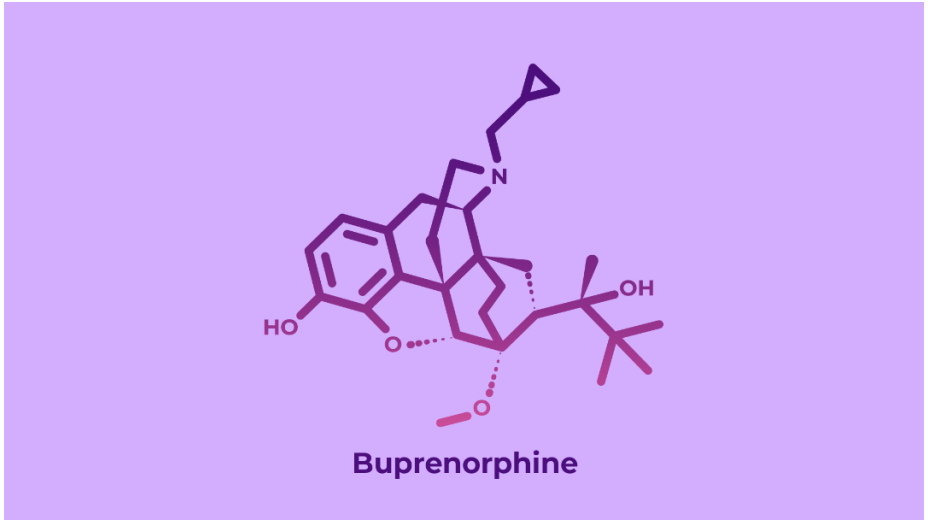
Thank you!
Questions & Discussion



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