BUPRENORPHINE FOR ANALGESIA

ADDRESSING CHRONIC PAIN AMIDST THE OPIOID CRISIS

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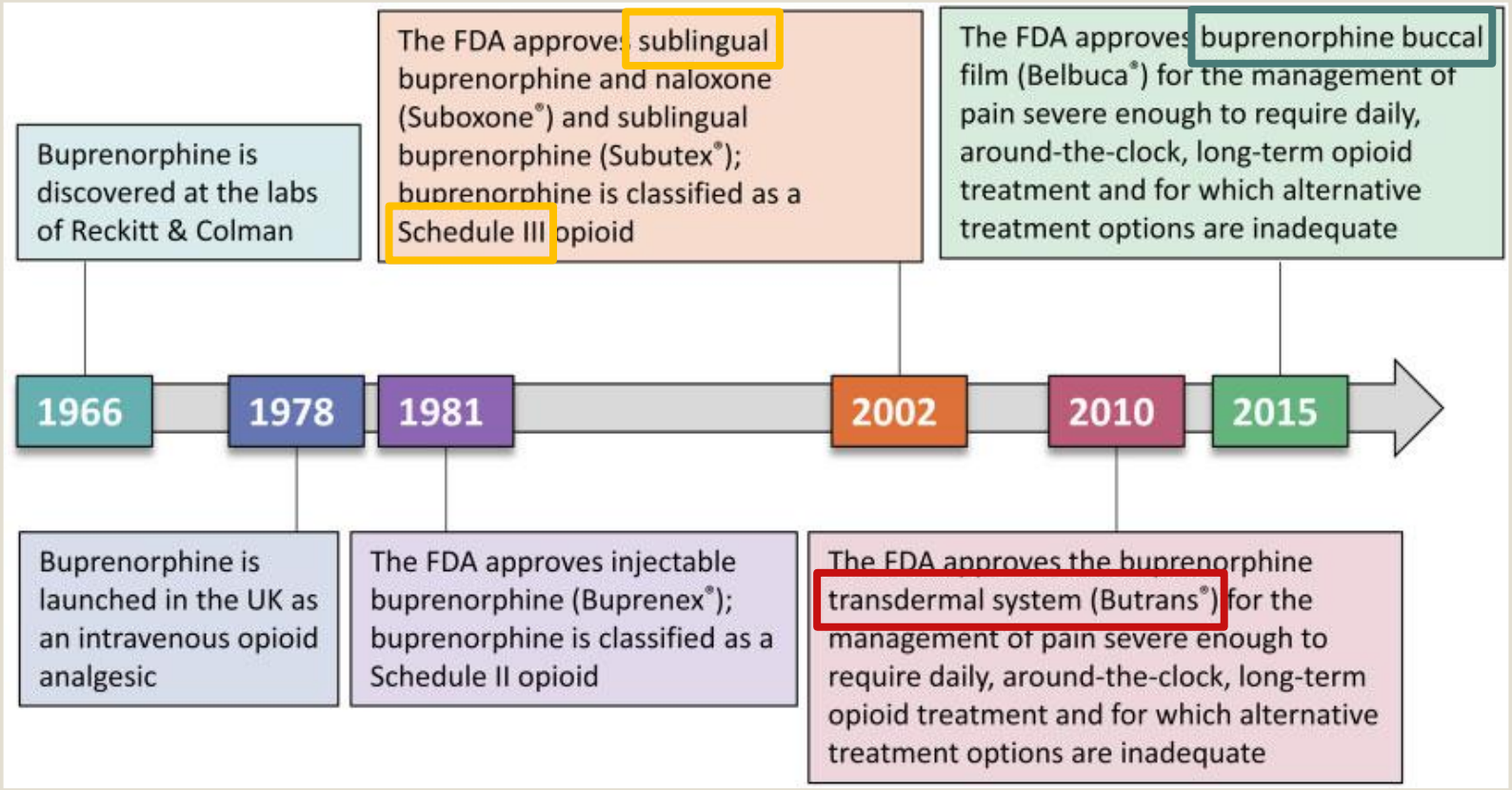
Disclosures

- No conflicts of interest to disclose
- Trade names may be used to differentiate form/routes
  - Generics are unavailable for most forms
- The information here is presented through the background of a palliative medicine provider
  - It is intended to be generalizable though other prescriber practices may differ
- Palliative medicine as a field treats the symptoms of serious, life-threatening illness and helps patients navigate their illness with their self, family, and medical teams
  - In treating cancer-related pain, opioid prescribing may be more aggressive than for chronic, non-malignant pain

Goals

- Learn the essential pharmacology of buprenorphine
- Learn clinical scenarios in which to use buprenorphine for analgesia
- Learn the forms of buprenorphine most suitable for analgesia
- Learn how to initiate buprenorphine, titrate, rotate between forms, and rotate off buprenorphine when managing pain

Buprenorphine – History



Webster 2020

Recent Updates

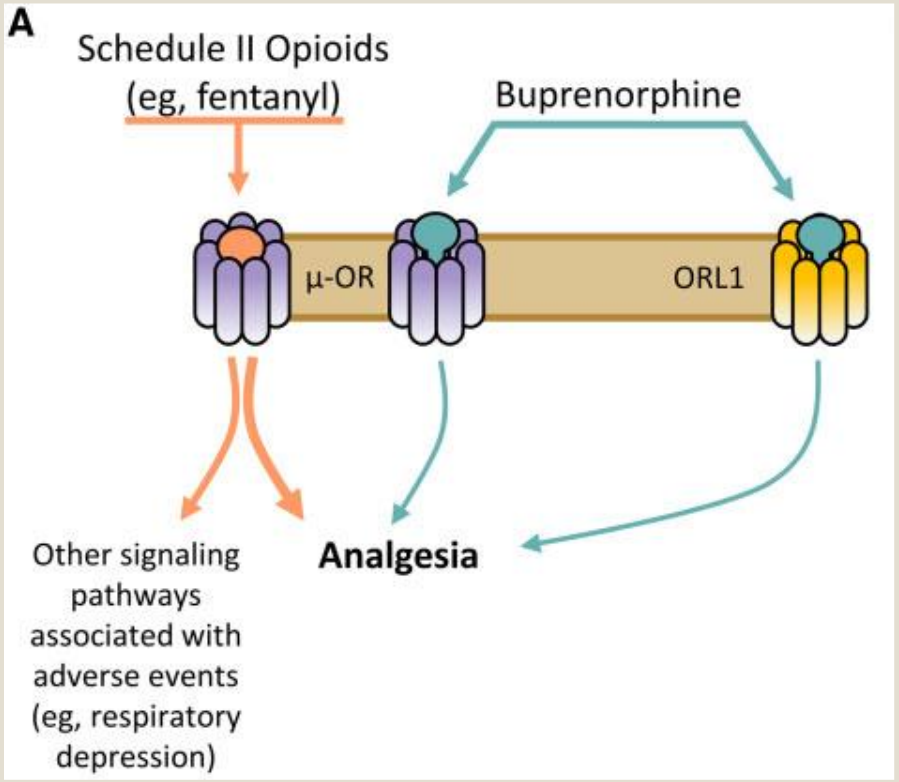
- 2023:
- Consolidated Appropriations Act of 2023
  - Eliminated the X-waiver to prescribe buprenorphine for opioid use disorder (OUD)
- Medication Access and Training Expansion (MATE) Act
  - Mandated an 8-hour training in OUD, substance use disorder (SUD), and/or pain to prescribe all schedule II-V meds

Pharmacology – Overview

- Buprenorphine aka Bup (pronounced “bupe”):
- Mixed opioid-receptor activity, “Partial” agonist
  - mu-opioid receptor agonist (effective for pain)
  - kappa- and delta-opioid receptor antagonist (limited respiratory depression and side effects)
- Very high binding affinity
- Long-acting

- Takeaway: efficacious and safer, but can interact with other opioids

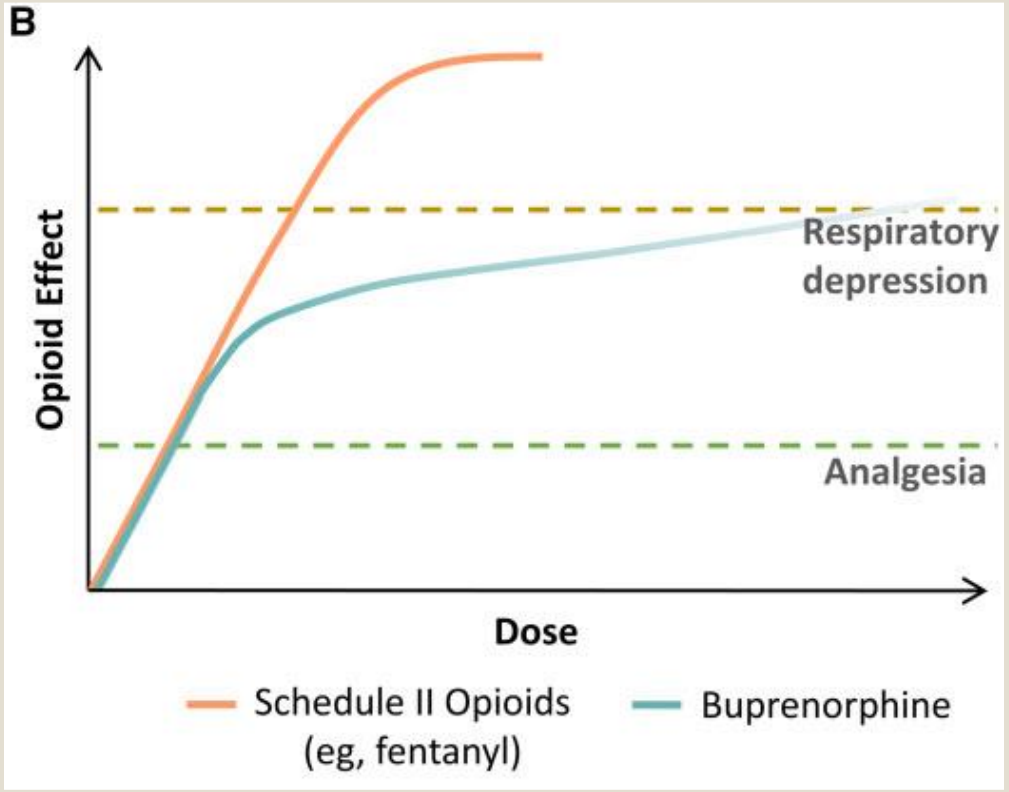
Pharmacology – Efficacy



Webster 2020

- Acts on the mu-opioid receptor, like other opioids
- Also acts on the opioid receptor-like 1 (ORL1) receptor
- Produces equally-efficacious analgesia
  - (Raffa 2014)

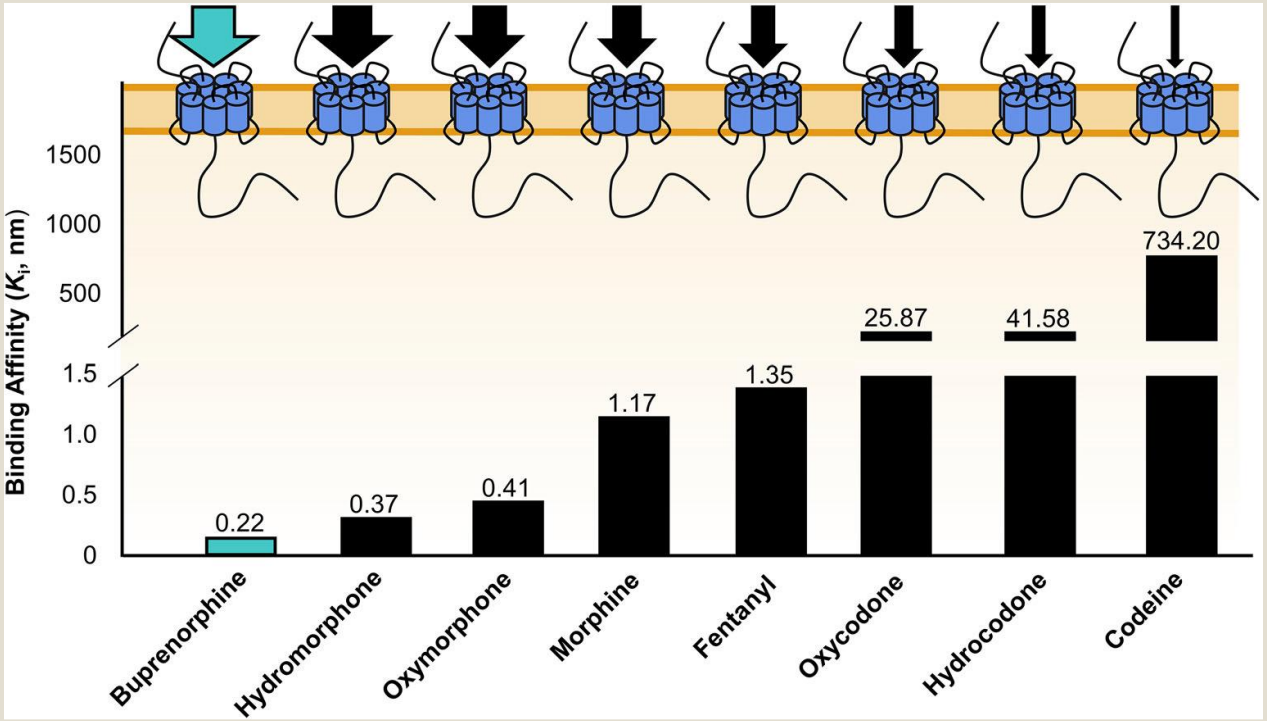
Pharmacology – Side Effects



Webster 2020

- Antagonist at the kappa- and delta-opioid receptors
- Limited respiratory depression; overdose on buprenorphine alone is not fatal in adults
  - Caution: Synergistic depression with benzodiazepines, z-drugs, alcohol, muscle relaxants, gabapentinoids, TCAs

Pharmacology – Affinity



Volpe 2011 & Gudin 2020

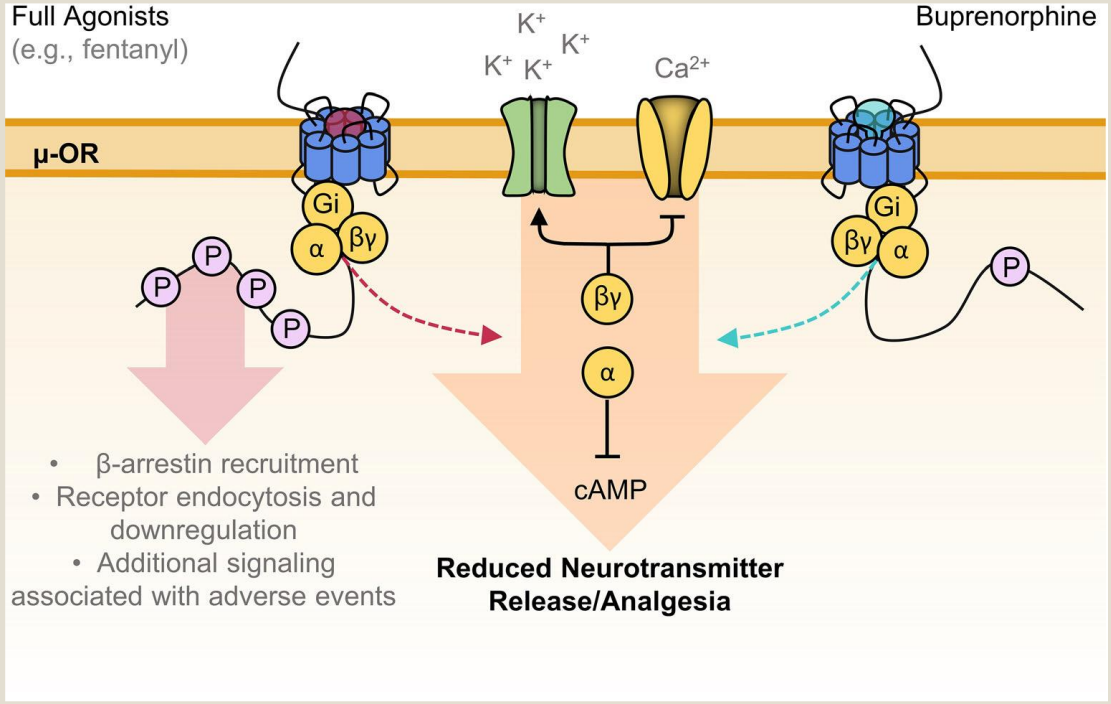
- High receptor binding affinity
- Can compete with other opioids for the mu-opioid receptor

Receptor Occupancy/Availability

	Buprenorphine total daily dose	1 mg	2 mg	4 mg	8 mg	12 mg	16 mg	24 mg	32 mg
Estimated mu-OR availability	based on in vivo effect of heroin (Comer 2005)		**21 – 31%**		**11 – 22%**				**6 – 12%**
	based on functional MRI (Greenwald 2014)	71 – 85%	**53 – 72%**	36 – 55%	20 – 35%	13 – 24%	**9 – 20%**	4 – 15%	**2 – 12%**

(non-bolded numbers indicate data extrapolated from a curve)

Pharmacology – Tolerance



Gudin 2020

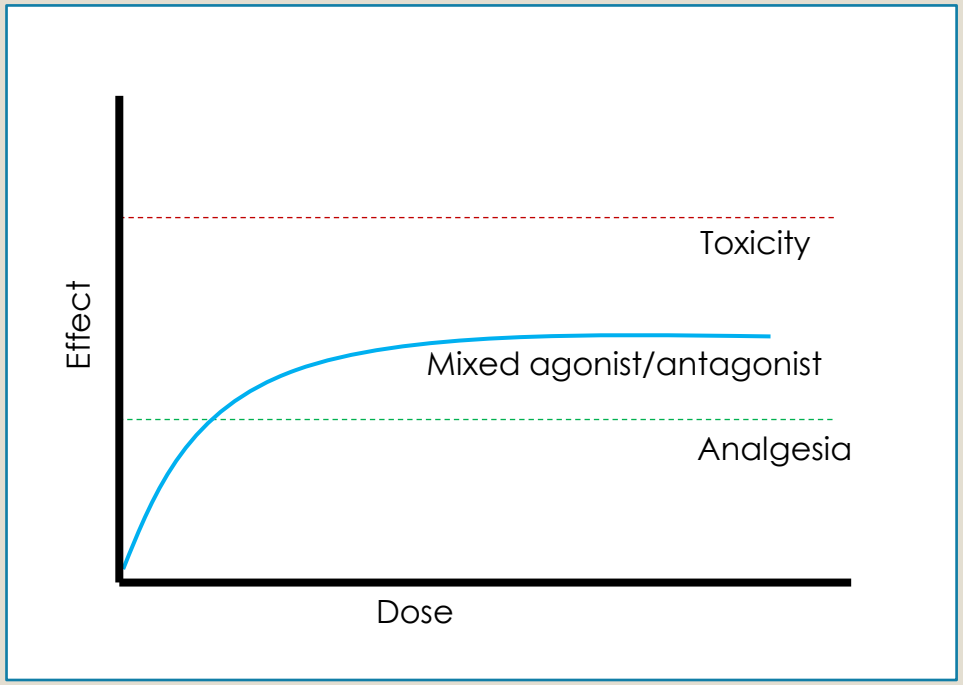
- Less beta-arrestin recruitment leads to:
  - Less tolerance
  - Less respiratory depression, constipation, and abuse potential

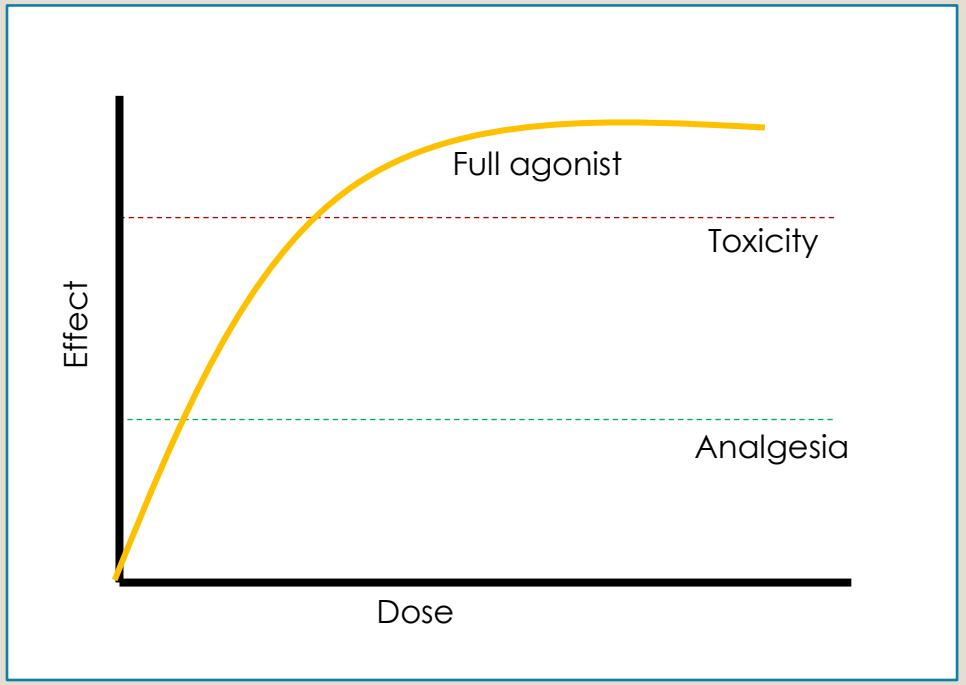
Summary of Attributes

- Effective analgesia
- Relative ceiling on respiratory depression
  - Fatal overdose limited but possible with other non-opioid respiratory depressants
- Less dysphoria, sedation, constipation
- Limited tolerance
- Limited abuse potential and withdrawal
- Reduced endocrinopathies
- Convenient dosing schedule

- It's better than the rest.

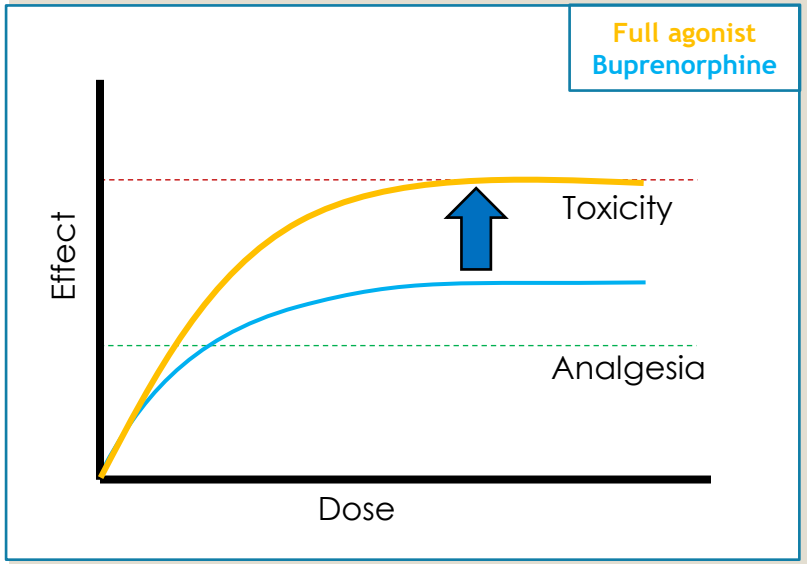
Inter-Opioid Interactions





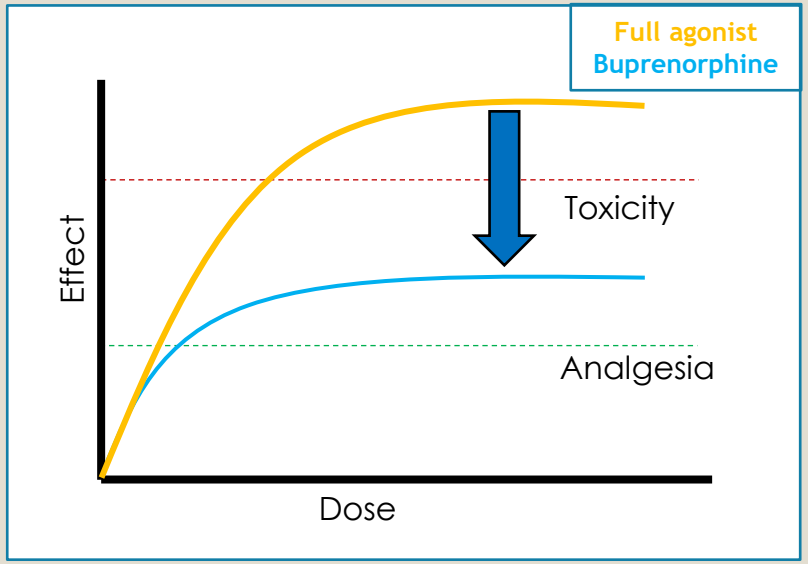
Inter-Opioid Interactions

Buprenorphine followed by full agonist



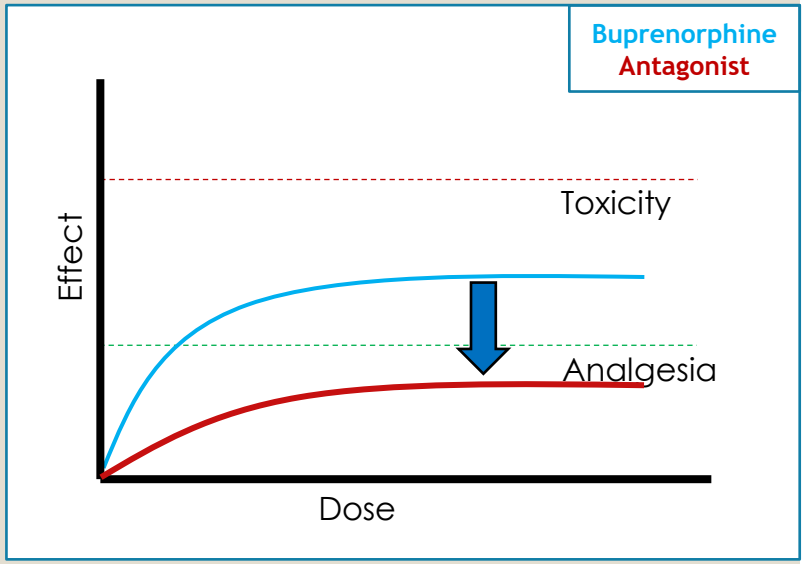
Decreased/blocks effect of full agonist

Full agonist followed by buprenorphine



Buprenorphine displaces full agonist potentially resulting in precipitated withdrawal (due to kappa/delta antagonism of bup)

Buprenorphine followed by antagonist



Buprenorphine remains on receptor with slowed antagonist effect

Common Adverse Effects

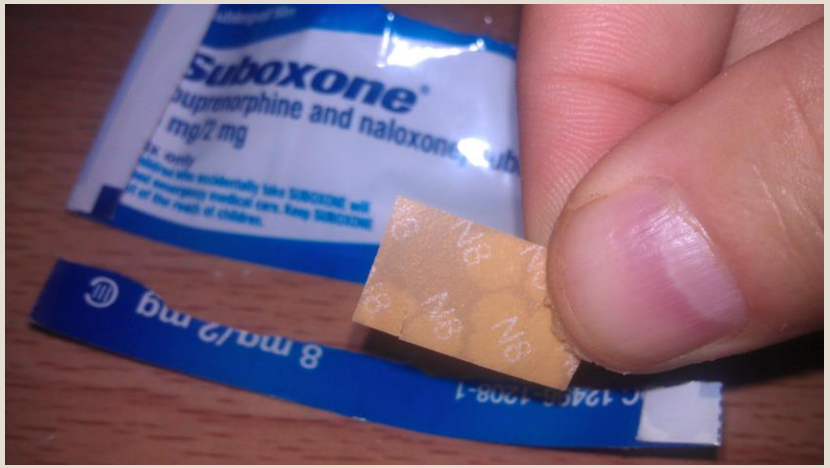
- Similar to typical opioids:
  - Constipation
  - Nausea
  - Headache
  - Pruritis
  - Euphoria/Dysphoria
- Unique to buprenorphine:
  - Transdermal – Rash
  - Sublingual and buccal – dental carries
  - Sublingual, high dose – edema

Pharmacokinetics

- Highly lipophilic, 96% globulin-protein bound
- Primarily excreted via bile and stool
- Hepatic metabolism
  - CYP3A4 (phase 1) → nor-buprenorphine
    - High affinity agonist for mu, kappa, and delta-opioid receptors
    - Poor blood-brain-barrier penetration
    - Hydrophilic; removed via urine
  - Glucuronidation (phase 2)
    - Affects both buprenorphine and nor-buprenorphine
    - Inactivates them
  - Extensive first pass metabolism = poor oral bioavailability

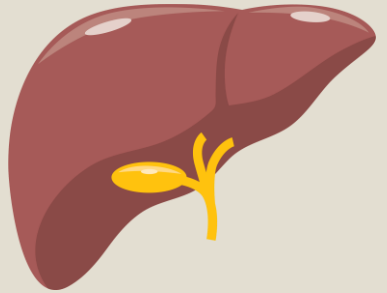
Buprenorphine-Naloxone (Suboxone)

- Don't worry about the naloxone (Nx)
  - Naloxone = opioid antagonist
  - Minimal SL or oral bioavailability, no effect on analgesia of Suboxone
  - When liquefied and injected intravenously, naloxone blunts the euphoric effect
  - Purpose: deterrent for misuse

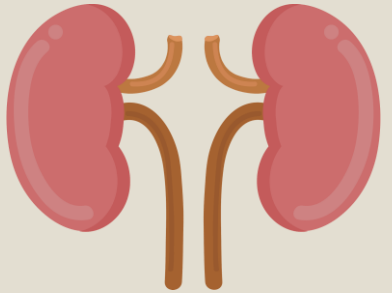


Specific Populations

- Liver impairment
  - Safe in mild-moderate liver impairment (Child-Pugh A/B)
  - In severe liver disease, phase-II metabolism preserved (glucuronidation)
  - Decrease dose by 50%, decrease dose frequency, and avoid naloxone in Child-Pugh C – not studied directly
    - Naloxone is bioavailable via oral route in severe liver impairment



- Renal impairment
  - Safe in any level of renal impairment
  - Plasma concentration unchanged in hemodialysis
  - Norbuprenorphine does not accumulate in renal failure



Specific Populations

- Pregnancy
  - Preferred opioid
  - Maternal – clinically insignificant
  - Neonates – can cause neonatal opioid withdrawal syndrome like other opioids, however it has the lowest risk
  - Low levels in breast milk – considered safe, monitor infants

- Older adults
  - Transdermal testing revealed clearance does not change with age
  - Less sedation, cognitive impairment, and risk of fractures compared to other opioids

Specific Populations

- Children
  - Indications:
    - Acute pain – intravenous form
    - OUD – SL and subdermal implant forms
  - No FDA approval for chronic pain
    - There are reports of successful use of SL and TD bup in pediatric patients for chronic pain (Attinà 2021)
  - Toxicity concerns
    - Toxicity in children including overdose is reported in the literature; does appear safer than other opioids
    - Caution should be exercised with dosing and titration if this medicine is chosen

When to Choose

- Honestly, first line for most patients needing an opioid

- Pain severe enough to warrant opioids
- Poor efficacy with opioids
- Side effect burden from opioids
- Older adults, renal impairment, liver impairment, pregnant
- High risk of harm with opioids - history of substance use disorder or difficulty with managing meds
- Ease of access - Schedule III

Forms

- Intravenous (IV)/Intramuscular (IM) (**Buprenex**)
- Transdermal (TD) patch (**Butrans**)
- Buccal film (**Belbuca** for pain; Bunavail for OUD)
- Sublingual (SL) film/tablet (**Suboxone**, **Subutex**, Zubsolv)
- Long-acting injectable (Sublocade, Probufine, Brixadi)

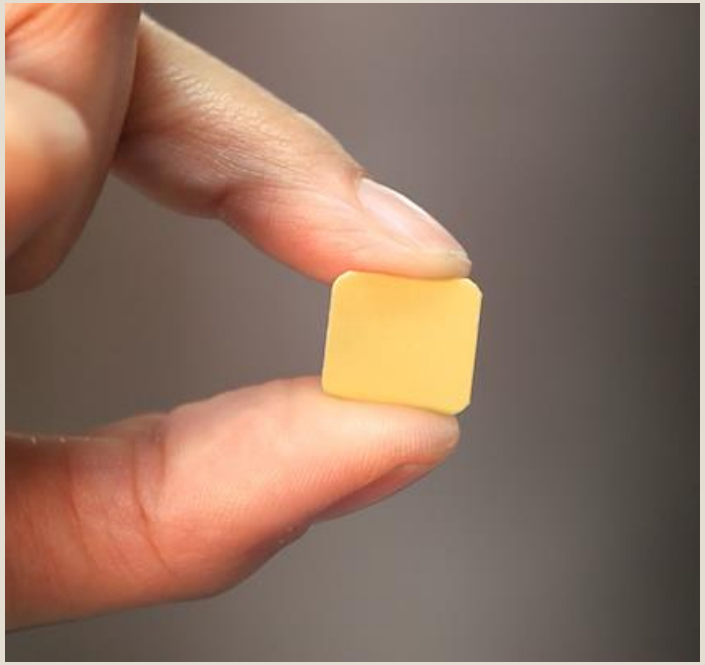
(Forms commonly used for pain are bolded)

Transdermal Buprenorphine (Butrans)

- FDA approval: chronic pain
- Dosing strengths:
  - 5, 7.5, 10, 15, and 20 mcg/hour patches available
  - Limited to 20 mcg/hr due to unpublished "risk" of QTc prolongation: 9.2 ms
  - Transtec (Europe) patches up to 70 mcg/hr
- Change patch every 7 days
  - Initial patch reaches analgesic steady state in 72 hours
  - Wait minimum 3 weeks before reapplying to same site
- Consider alternative if MEDD >80 OMEs
  - (morphine equivalent daily dose)
  - (oral morphine equivalents)

Buccal Buprenorphine (Belbuca)

- FDA approval: chronic pain
- Dosing strengths:
  - 75, 150, 300, 450, 600, 750, 900 mcg
  - Manufacturer recommended maximum dose: 900 mcg BID
- Dosed BID and takes 4 days to reach steady state
- Consider alternative if MEDD >160
- Oral mucositis present?
  - Okay to utilize
  - Reduce dose by 50%
- Requires good oral hygiene habits
  - 2022 FDA warning for periodontal disease



Sublingual Buprenorphine (Suboxone, Subutex)

- FDA approval: opioid use disorder, off-label for pain
- Dosing strengths:
  - 2-0.5, 4-1, 8-2, 12-3 mg (Bup-Nx aka Suboxone) or 2, 8 mg (Subutex)
  - Split 2 mg films give: 0.25 mg (1/8 film), 0.5 mg (1/4 film) or 1 mg (1/2 film)
    - Okay to cut films (Reindel 2019)
  - QTc prolongation up to 5.4 ms with doses 16 to 32 mg daily
- Dosed BID to QID for pain, usually TID
  - Sublingual absorption and distribution rate is variable between patients
- Requires good oral hygiene habits
  - 2022 FDA warning for periodontal disease
- Citrus helps cut the flavor
- A note to pharmacy may help
  - It is okay to cut the films
  - Doses of buprenorphine less than 8 mg per day are not expected to interfere significantly with a co-prescribed full-opioid agonist

Intravenous Buprenorphine (Buprenex)

- FDA approval: moderate to severe acute pain
- Dosing strength:
  - 0.3 mg/1 mL ampule (300 mcg)
  - Approximately 10 OME, may be equivalent to up to 30 OME
  - Repeat dose once after 30-60 minutes
- Pharmacodynamics
  - Onset 5-15 minutes, peak 60 minutes, duration 6-8 hours
- Not for long-term use

Pharmacies and Cost

- Suboxone usually widely available and cheapest
  - List prices for 30 films of 2 mg is $169.79 or 8 mg is $324.49
  - Most pharmacies will carry
  - Insurance will often cover completely without a prior authorization
- Butrans may be difficult to get filled
  - List prices for 4 patches of 5 mcg/h is $283.49, 20 mcg/h is $752.89
  - Henry Ford pharmacies usually stock it
  - Insurance may cover but sometimes require a prior authorization and then cover most to all the cost
- Belbuca is often challenging to get filled
  - List prices for 60 films of 150 mcg is $393.49, 900 mcg is $969.91
  - Also available at Henry Ford pharmacies if approved
  - Insurances less often cover initially; more often requires a prior authorization for coverage
  - Many insurance plans do not include it in their formulary; it will likely not be covered in these cases

Equivalence

Buprenorphine	Oral Morphine Equivalent/24hrs (OME)								
	7	15	30	48	60	80	100	120	300
Transdermal (TD) patch	5mcg/hr q7days		10mcg/hr q7days	20mcg/hr q7days					
Buccal patch	75mcg daily	150mcg q12hrs	300mcg q12hrs	450mcg q12hrs	600mcg q12hrs	750mcg q12hrs		900mcg q12hrs	
Sublingual (SL) tabs or films			0.25mg TID	0.5mg TID (split 2 mg films)		1mg BID (split 2mg tabs)		1mg TID	2mg TID

Case 2021, with additions by presenter

Equivalence

There are not universally agreed upon conversion factors from oral morphine to buprenorphine

These listed below are to convert TO bup, rather than FROM bup

Bioavailability determines OME: buprenorphine ratio

- TD patch and IV – 100:1 ratio ("100%" bioavailable)
  - Transdermal dose is the dose delivered to blood though bioavailability is 15%
- Buccal form – 50:1 ratio (roughly 46-65% bioavailable)
- Sublingual form – 30:1 ratio (roughly 30-50% bioavailable)

Bioavailability determines ratio between buprenorphine forms

- TD Patch: Buccal – 1:2 ratio (100%:50% bioavailable)
- TD Patch: Sublingual – 1:3 ratio (100%:30% bioavailable)
- Buccal: Sublingual – 0.6:1 ratio (50%:30% bioavailable)

Rotation: Target Dose

- Start rotation to bup by calculating the total daily dose:
  - Add up daily OME (aka MEDD)
  - Identify preferred bup form within MEDD range
  - Use appropriate ratio to calculate bup total daily dose
  - Divide total daily dose into appropriate dosing schedule (for buccal/sublingual)

Of note:

- When using bup for pain only (normal risk, without OUD), adequate doses are:
  - Often well within the ranges covered by the forms approved for pain
  - Often no greater than **1800 mcg buccal bup/day** or **3 mg SL bup/day**
- When using bup for patients with high risk, OUD, SUD, or for harm-reduction:
  - Higher daily doses (12, 16, 24 mg SL bup per day) may be necessary to control pain adequately

Rotation Methods – TD & Buccal

- Opioid-naïve patients
  - TD and buccal bup can be started at the lowest doses
- Opioid-tolerant patients
  - Stop long-acting, scheduled full opioids. Short-acting, as-needed full opioids can be continued
  - Start TD or buccal bup at appropriate initial dose and titrate to effect
    - Official prescriber information recommends starting no higher than 10 mcg/h or 300 mcg bid, respectively
  - Once the analgesic goal is attained, short-acting full opioids can be stopped. In some cases, there is a role to continue them for breakthrough pain

TD Target Dose Estimation

- Rule of Thumb/Quick Estimation
  - For experienced providers
  - For patients on short-acting opioids (hydrocodone or oxycodone) up to 10 mg per dose
  - A rough way to determine starting dose for Butrans is to start with the same "number" dose as the patient is prescribed
  - For example:
    - Pain is well-controlled with Hydrocodone 5 mg? Start Butrans at 5 mcg/h
    - Hydrocodone 5 mg is not controlling pain? Start Butrans at 7.5 or 10 mcg/h
    - Pain is well-controlled with Oxycodone 10 mg? Start Butrans at 10 mcg/h
    - Uptitration after initiation may still be needed

Rotation Methods – Sublingual

- Full-Dose Initiation aka Stop-Start Method
  - Original induction method of Suboxone for patients with OUD
  - Premise
    - Patient stops all opioids
    - Wait for mild-moderate withdrawal
    - Take a full dose of Suboxone (for OUD, often 2 to 8 mg)
  - Concern
    - If patient is opioid-tolerant and on opioids

      -And-
    - If patient is not already in some withdrawal
    - Then:
      - A single 1.5-2 mg dose of buprenorphine can precipitate withdrawal

Rotation Methods – Sublingual

- Low-Dose Initiation aka Bernese Method aka Micro-Dose Induction
  - Avoids withdrawal or gaps in opioids for pain
  - Premise
    - Patient continues all their current full/typical mu-opioid agonists
    - Bup is taken in increasing doses daily
    - Once the patient reaches the target dose of bup, stop all other opioids (works for OUD or pain)
- In-Between: Pain Stop/Start aka "Low-Dose Full" Initiation aka Combined Method
  - Fastest initiation method for select patients
    - For patients not on long-acting opioid with an MEDD less than 120 OMEs
    - For pain only, when each dose of bup to be taken is no greater than 1 mg (regardless of dose frequency)
  - Premise
    - Patient takes their short-acting typical opioid
    - Wait 6-8 hours without taking it again
    - Bup is given at the target dose
    - (the other opioid is generally stopped at this point)

How We Low-Dose, Outpatient

Day #	Bup dose and schedule	Suboxone film size	Bup total daily dose	Full mu-opioid agonists
Day 0	No Bup	No Suboxone	0 mg	Continue full mu-opioid agonists at the original dose
Day 1	0.5 mg SL BID	1/4 film (2-0.5 mg)	1 mg	
Day 2	0.5 mg SL TID	1/4 film (2-0.5 mg)	1.5 mg	
Day 3	1 mg SL BID	1/2 film (2-0.5 mg)	2 mg	
Day 4 *	1 mg SL TID	1/2 film (2-0.5 mg)	3 mg	Stop full mu-opioid agonists on Day 4 (or later as below) for pain only or Day 8 for high-risk patients
Day 5	2 mg SL BID	Full film (2-0.5 mg)	4 mg	
Day 6	2 mg SL TID	Full film (2-0.5 mg)	6 mg	
Day 7	4 mg SL BID	2 full films (2-0.5 mg)	8 mg	
Day 8	4 mg SL TID	2 full films (2-0.5 mg)	12 mg	
Optional titration	4 mg QID to 8 mg TID or QID	Full film (4-1 mg or 8-2 mg)	16 to 32 mg	

* Consider holding at Suboxone 1 mg TID for several days before increasing

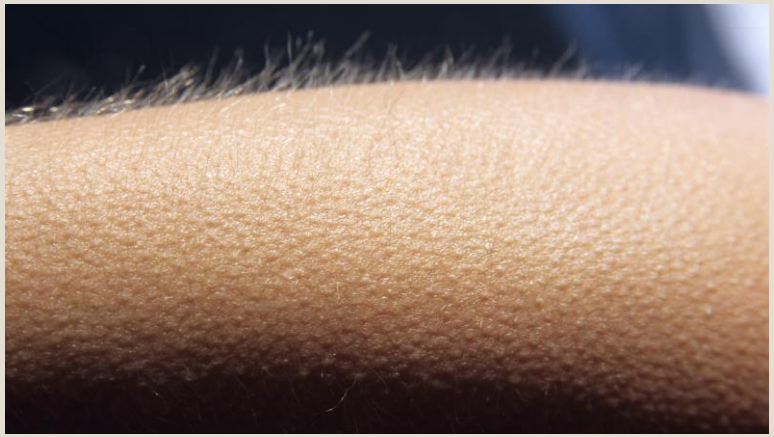
How We Low-Dose, Inpatient

Day #	Bup dose and schedule	Belbuca film or Subutex tablet size	Equivalent SL total daily dose	Full mu-opioid agonists
Day 0	No Bup	No buprenorphine	0 mg	Continue full mu-opioid agonists at the original dose
Day 1, Dose 1	150 mcg buccal	150 mcg Belbuca film		
Day 1, Dose 2	300 mcg buccal	300 mcg Belbuca film		
Day 2, Dose 1	450 mcg buccal	450 mcg Belbuca film	1.5 mg **	
Day 2, Dose 2	600 mcg buccal	600 mcg Belbuca film		
Day 3 *	900 mcg buccal BID	900 mcg Belbuca film	3 mg ***	Stop full mu-opioid agonists on Day 3 (or later as below) for pain only or Day 7 for high-risk patients
Day 4	2 mg SL BID	Full 2 mg tablet	4 mg	
Day 5	2 mg SL TID	Full 2 mg tablet	6 mg	
Day 6	4 mg SL BID	2 full 2 mg tablets	8 mg	
Day 7	4 mg SL TID	2 full 2 mg tablets	12 mg	
Optional titration	4 mg QID to 8 mg TID or QID	2 full 2 mg tablets or full 8 mg tablet	16 to 32 mg	

* Consider holding at Belbuca 900 mcg for several days before increasing
** Belbuca 450 mcg BID is equivalent to Suboxone 0.5 mg (1/4 films) TID
*** Belbuca 900 mcg BID is equivalent to Suboxone 1 mg (1/2 films) TID

Precipitated Withdrawal

- Withdrawal can be caused by the initial dose(s) of buprenorphine during full dose induction
  - Due to high doses of buprenorphine utilized when treating OUD
  - Our low-dose initiation schedule is conservative and cautious to avoid this issue
- Multiple case reports suggest this can be managed by administering repeated doses of buprenorphine 8 mg SL



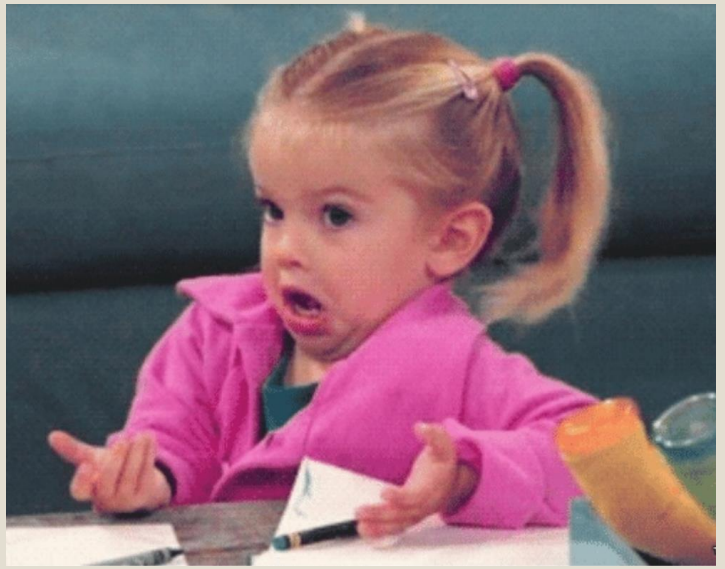
Titration

- Increase as you usually would, giving time to reach steady state
- Pain is mild to moderately uncontrolled?
  - Increase dose by 25-50%
- Pain is moderate to severely uncontrolled?
  - Increase dose by 50-100%
- With sublingual forms, consider following the low-dose induction table for the next step OR first increase frequency (up to QID) to increase the total daily dose
- Sublingual form has a soft dosing limit of 24 mg per day
  - Insurance may not cover more, MI tracks patients on higher doses

- Decrease as you usually would
  - Dose reduce about 25% every two weeks to few months

Quirk

- Of note, most patients on the right dose of buprenorphine do not require breakthrough opioids



Rotation Off Buprenorphine

- Consider the reason for the rotation
  - Remember the initial reason for choosing bup for the patient in question
  - Nociplastic pain? Harm reduction? These patients may not benefit more from a different opioid

- No universal methods. Start low, go slow.
- Patient on lower dose of buprenorphine (mcg)
  - Treat as opioid naïve
- Patient on higher dose of buprenorphine (mg)
  - True opioid tolerance is unclear, especially with very high mg doses (8 to 32 mg total daily dose)
  - Avoid using the previous equivalence ratios
    - (i.e. 12 mg bup x 30 (ratio 1:30) would give 360 MEDD; this likely overestimates the true opioid tolerance)

Rotation Off Buprenorphine

- Rotating off a higher dose of bup using a short-acting opioid:
  - Start a typical/full agonist short-acting opioid PRN (consider hydromorphone due to receptor affinity) and allow liberal use
  - Stop buprenorphine
  - Buprenorphine will wash out over 3 days
  - Use the PRN doses needed on day 3 to estimate long-acting dose
  - Initiate long-acting typical/full agonist opioid on day 4
- Rotating a higher dose of bup to methadone:
  - Swap a dose of buprenorphine for a dose of methadone every 3-7 days
    - Example: Prior to rotation buprenorphine 4-4-4 mg
    - Day 1 of rotation: Methadone 5 mg, buprenorphine 4-4 mg
    - Day 4-7 of rotation: Methadone 5-5, buprenorphine 4 mg
    - Day 7-14 and on (completion): Methadone 5-5-5 mg

Perioperative Management

- Kohan et al (2021) say it better than I can:
  - "Buprenorphine should not be routinely discontinued in the perioperative setting."
  - "Buprenorphine can be initiated in untreated patients with OUD and acute pain in the perioperative setting."
- If acute pain is uncontrolled in the perioperative setting while the patient is on buprenorphine, options include:
  - Use multimodal analgesic medications or interventions
  - Patient on lower doses of buprenorphine (e.g., ≤16 mg)?
    - Increase the dose of buprenorphine or give additional PRN doses
  - Continue buprenorphine at the current dose and add a high-affinity full agonist
  - Patient on higher doses of buprenorphine (e.g., ≥16 mg)?
    - Lower the dose of buprenorphine and add a full agonist as above

Special Thanks

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References

- Attinà G, Romano A, Triarico S, Mastrangelo S, Maurizi P, Ruggiero A. Transdermal buprenorphine for pain management in children. Drugs Context. 2021 Sep 14;10:2021-6-1. doi: 10.7573/dic.2021-6-1. PMID: 34567202; PMCID: PMC8443125.
- **Case AA, Kullgren J, Anwar S, Pedraza S, Davis MP. Treating Chronic Pain with Buprenorphine-The Practical Guide. Curr Treat Options Oncol. 2021 Nov 18;22(12):116. doi: 10.1007/s11864-021-00910-8. PMID: 34791564.**
- Comer SD, Walker EA, Collins ED. Buprenorphine/naloxone reduces the reinforcing and subjective effects of heroin in heroin-dependent volunteers. Psychopharmacology (Berl). 2005 Oct;181(4):664-75. doi: 10.1007/s00213-005-0023-6. Epub 2005 Sep 29. PMID: 16025322; PMCID: PMC4079466.
- **Davis MP. Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. J Support Oncol. 2012 Nov-Dec;10(6):209-19. doi: 10.1016/j.suponc.2012.05.002. Epub 2012 Jul 17. PMID: 22809652.**
- Greenwald MK, Comer SD, Fiellin DA. Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. Drug Alcohol Depend. 2014 Nov 1;144:1-11. doi: 10.1016/j.drugalcdep.2014.07.035. Epub 2014 Aug 19. PMID: 25179217; PMCID: PMC4252738.
- Gudin J, Fudin J. A Narrative Pharmacological Review of Buprenorphine: A Unique Opioid for the Treatment of Chronic Pain. Pain Ther. 2020 Jun;9(1):41-54. doi: 10.1007/s40122-019-00143-6. Epub 2020 Jan 28. PMID: 31994020; PMCID: PMC7203271.
- Kohan L, Potru S, Barreveld AM, Sprintz M, Lane O, Aryal A, Emerick T, Dopp A, Chhay S, Viscusi E. Buprenorphine management in the perioperative period: educational review and recommendations from a multisociety expert panel. Reg Anesth Pain Med. 2021 Oct;46(10):840-859. doi: 10.1136/rapm-2021-103007. Epub 2021 Aug 12. PMID: 34385292.
- Raffa RB, Haidery M, Huang HM, Kalladeen K, Lockstein DE, Ono H, Shope MJ, Sowunmi OA, Tran JK, Pergolizzi JV Jr. The clinical analgesic efficacy of buprenorphine. J Clin Pharm Ther. 2014 Dec;39(6):577-83. doi: 10.1111/jcpt.12196. Epub 2014 Jul 29. PMID: 25070601.
- Reindel KL, DeAngelis MJ, Ferrara AS, Conn KM, Phillips EM, Corigliano AT, Zhao F. An Exploratory Study of Suboxone (Buprenorphine/Naloxone) Film Splitting: Cutting Methods, Content Uniformity, and Stability. Int J Pharm Compd. 2019 May-Jun;23(3):258-263. PMID: 31085795.
- Spadaro A, Long B, Koyfman A, Perrone J. Buprenorphine precipitated opioid withdrawal: Prevention and management in the ED setting. Am J Emerg Med. 2022 Aug;58:22-26. doi: 10.1016/j.ajem.2022.05.013. Epub 2022 May 14. PMID: 35623179.
- Volpe DA, McMahon Tobin GA, Mellon RD, Katki AG, Parker RJ, Colatsky T, Kropp TJ, Verbois SL. Uniform assessment and ranking of opioid μ receptor binding constants for selected opioid drugs. Regul Toxicol Pharmacol. 2011 Apr;59(3):385-90. doi: 10.1016/j.yrtph.2010.12.007. Epub 2011 Jan 6. PMID: 21215785.
- Webster L, Gudin J, Raffa RB, Kuchera J, Rauck R, Fudin J, Adler J, Mallick-Searle T. Understanding Buprenorphine for Use in Chronic Pain: Expert Opinion. Pain Med. 2020 Apr 1;21(4):714-723. doi: 10.1093/pm/pnz356. PMID: 31917418; PMCID: PMC7139205.

FIN!