Managing Buprenorphine Patients does NOT have to be Painful

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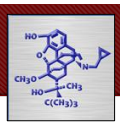
Disclosures

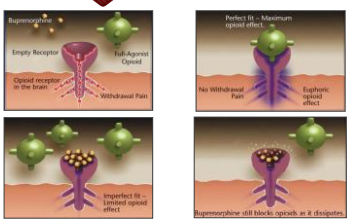
- Dr. Engle has nothing to disclose
- Dr. Cleary is a consultant for Kaleo Pharma and Remitigate, LLC

Objectives

- Review clinically relevant pharmacokinetic and pharmacodynamic properties of buprenorphine
- Discuss buprenorphine's role in therapy for both chronic pain management as well as medication assisted therapy (MAT)
- Develop an acute pain management plan for a patient being maintained on buprenorphine for MAT

What is buprenorphine

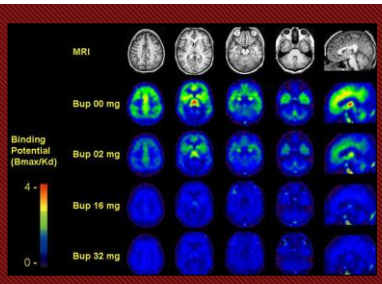




Partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor

Dehydroxylated phenanthrene

NAABT. Buprenorphine. A treatment for opioid addiction in the privacy of a doctor's office. (2015)



http://www.naabt.org/images/petscan.jpg

Efficacy and adverse effects of buprenorphine in acute pain management: systematic review and meta-analysis of randomised controlled trials.
L.D. White1,2, *, A. Hodge2 , R. Vlok3,4 , G. Hurtado2 , K. Eastwood2 and T. M. Melhuish
Br J Anaesth. 2018 Apr;120(4):668-678

What is buprenorphine?

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Buprenorphine Education: Technical Explanation NAABT (2018).

Pharmacokinetics

- Absorption
  - Not absorbed enterally due to significant first pass metabolism
  - Highly lipophilic
  - Well absorbed by oral mucosa
- Bioavailability
  - SL Tablet: 31%
    - Zubsolv 5.7/1.4 mg = other SL tabs bup 8/2 mg
  - SL Film: *"Relative increase in exposure of sublingual film compared with sublingual tablets"*
  - Buccal Film: 46 – 65 %
    - BUNAVAIL 4.2/0.7 mg buccal film = SUBOXONE 8/2 mg sublingual tablet
  - Butrans patch: ~15%

- LARGE volume of distribution if adults that is highly variable (97-187 L/kg)
- Onset of action of analgesia for IM ≥15 minutes

Buprenorphine. Lexi-Drugs. In Lexicomp Online

Pharmacokinetics

- Metabolism
  - Hepatic
    - *Avoid use in severe liver disease*
    - Substrate: *CYP3A4 (major)-> norbuprenorphine (active metabolite)-> 3-o-glucuronide via UGT1A3
      *pharmacogenetically variable
- Time to peak
  - Buccal 2.5-3 hours
  - SL 0.5-1 hour
  - Patch ~3 days until steady state
- Mean Elimination Half-Life
  - 24 - 48 hours
    - slow dissociation from mu receptors prolongs effective half life

Buprenorphine. Lexi-Drugs. In Lexicomp Online

Pharmacodynamics

- Common side effects at therapeutic doses: headache, dry mouth, constipation
- Side effects at **supra**therapeutic doses
  - lethargy, a medicated feeling (described as " cloudy" "foggy" or " slow"), tiredness, nausea, constricted pupils in low light, a general unmotivated feeling, unjustified feeling of contentment, dehydration (indicated by dark urine)
- Side effects at **sub**therapeutic doses
  - Sweating, chills, goose bumps, dilated pupils in normal light, diarrhea, cramps, insomnia, nausea, anxiety, depression, dehydration, cravings
- Precautions: similar to other opioids

Samhsa.gov . *Medication and Counseling Treatment (2018)*

Clinically Relevant Pharmacokinetics

"We give narcan (naloxone) to reverse opioid overdose.

Suboxone contains both buprenorphine and naloxone.

Does this mean the patient goes into a little bit of withdrawal with each dose?"

No.

What is Buprenorphine

"If someone is taking opioids without me knowing it and I give them buprenorphine, will this precipitate withdrawal?"

Yes.

"If someone is taking buprenorphine without me knowing it and I give them opioids, will this precipitate withdrawal?"

No.

Buprenorphine Formulations *per Indication*

Medication Assisted Treatments (MAT)	Analgesics
Suboxone (buprenorphine/naloxone) SL film Generic available as of June 14, 2018 Subutex (buprenorphine) SL tablet Zubsolv (buprenorphine/naloxone) SL tablet Bunavail (buprenorphine/naloxone) buccal films Generic buprenorphine/naloxone SL tablet Sublocade (buprenorphine) subcutaneous injection once monthly Probuphine (buprenorphine) intradermal implant	Butrans Belbucca Buprenex Subutex (off-label use)

Buprenorphine in Chronic Pain Management

Medication Assisted Treatments

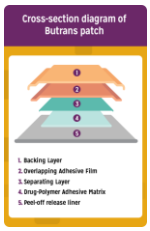
- Suboxone (buprenorphine/naloxone) SL film
  - Generic available as of June 14, 2018
- Subutex (buprenorphine) SL tablet
- Zubsolv (buprenorphine/naloxone) SL tablet
- Bunavail (buprenorphine/naloxone) buccal films
- Generic buprenorphine/naloxone SL tablet
- Sublocade (buprenorphine) subcutaneous injection once monthly
- Probuphine (buprenorphine) intradermal implant

Analgesics

- Butrans
- Belbucca
- Buprenex
- Subutex (off-label use)

Butrans

- Dosage forms: 5mcg, 7.5mcg, 10mcg, 15mcg, 20mcg / hour transdermal patch
  - Dosing capped at 20mcg/hr due to QTC prolongation… or does it?
- Two patches can be worn at once in two separate adjacent sites
- Rotate site every 7 days
- DO NOT CUT PATCH
- IR opioids indicated in the first 72 hours (time until steady state)
- Patient on >80mg MME of morphine NOT a candidate
- Hold patch for 72 hours if switching therapies



Belbuca

- Indicated for management of "pain requiring around-the-clock, long-term opioid treatment not adequately controlled by alternatives"

- Dosage forms: 75, 150, 300, 450, 600, 750, 900mcg
- Typically dosed BID
- Patient using >160mg MME of morphine NOT a candidate for Belbuca
- 30 minute dissolve time
- Butrans 20mcg/hour can be replaced by 150mcg q12 Belbuca
  - Not 100% equivalent due to absorption/bioavail differences

Subutex

- Off-label use in the treatment of chronic pain when full opioid agonists are not an option
- Dosage forms: 2mg and 8mg SL tablets
- Scheduled dosing regimen (typically BID)
  - Swallowing reduces bioavailability and increases GI intolerance
- NOT for opioid naïve patients-> documented deaths

Buprenex

- Indicated for moderate to severe acute pain (not for long-term use)
  - IM or slow IV 0.3mg every 6-8 ours PRN q6-8 hours; repeat 0.3mg may be repeated 30-60 minutes after initial dose if needed
- As of 3/13/2019 ASHP listed as active shortage due to manufacturing delays and increased demand
  - Ampules are available

What about dosing conversions…

- Complex PK/PD (as we just reviewed)
- Neither CDC nor CMS calculator recognize MME for buprenorphine
- Given its mechanism of action should buprenorphine be assigned an MME?

Buprenorphine in Pain Management

Medication Assisted Treatments	Analgesics
Suboxone (buprenorphine/naloxone) SL film Generic available as of June 14, 2018 Subutex (buprenorphine) SL tablet Zubsolv (buprenorphine/naloxone) SL tablet Bunavail (buprenorphine/naloxone) buccal films Generic buprenorphine/naloxone SL tablet Sublocade (buprenorphine) subcutaneous injection once monthly Probuphine (buprenorphine) intradermal implant	Butrans Belbucca Buprenex Subutex (off-label use)

Buprenorphine for MAT

FDA Labeled Indication

- For induction and maintenance treatment of opioid dependence
  - Prescribing requires DATA 2000 waiver to obtain DEA X license number

Therapeutic Role

- Lower the potential for misuse of heroin and other opioids
- Diminish the effects of physical dependency to opioids, such as withdrawal symptoms and cravings
- Increase safety in cases of overdose

SAMHSA Advisory, Sublingual and Transmucosal Buprenorphine for Opioid Use (2016)

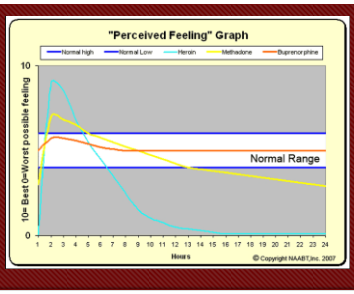
Buprenorphine for MAT

"A common misconception associated with MAT is that it substitutes one drug for another.

Instead, these medications relieve the withdrawal symptoms and psychological cravings that cause chemical imbalances in the body.

MAT programs provide a safe and controlled level of medication to overcome the use of an abused opioid."

Medication and Counseling Treatment | SAMHSA (2018)



http://www.naabt.org/fil/FeelingGraph.gif

Buprenorphine for MAT

"Medication Assisted Therapy (MAT), particularly with opioid agonist medications (eg. buprenorphine), has been found to reduce morbidity and mortality, decrease overdose deaths, reduce transmission of infectious disease, increase treatment retention, improve social functioning, and reduce criminal activity."

SAMHSA Advisory, Sublingual and Transmucosal Buprenorphine for Opioid Use Disorder. (2016)


Cochrane Library
Cochrane Database of Systematic Reviews

Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence (Review)

Mattick RP, Breen C, Kimber J, Davoli M

Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Background

Methadone is widely used as a replacement for illicit opioid use such as heroin in medically-supported opioid substitution maintenance programmes. Two other drugs have been used to help reduce illicit opioid use, specifically buprenorphine and LAAM (levo-alpha acetylmethadol). LAAM is not used in current clinical practice. Buprenorphine is currently used and can reduce illicit opioid use compared with placebo, although it is less effective than methadone. Buprenorphine is an opioid drug that is not as potent as heroin and methadone, although the effects of buprenorphine may last longer. Buprenorphine can be taken once every two days. The trials include different formulations of buprenorphine: sublingual solutions, sublingual tablets, combined buprenorphine/naloxone sublingual tablet and an implant.

Key results

The review of trials found that buprenorphine at high doses (16 mg) can reduce illicit opioid use effectively compared with placebo, and buprenorphine at any dose studied retains people in treatment better than placebo.

Buprenorphine appears to be less effective than methadone in retaining people in treatment, if prescribed in a flexible dose regimen or as a fixed and low dose (2 - 6 mg per day). Buprenorphine prescribed at fixed doses (above 7 mg per day) was not different from methadone prescribed at fixed doses (40 mg or more per day) in retaining people in treatment or in suppression of illicit opioid use.

Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence Cochrane Database of Systematic Reviews

Buprenorphine for MAT

- **The Induction Phase** is the medically monitored startup of buprenorphine treatment performed in a qualified physician's office or certified OTP using approved buprenorphine products. **The medication is administered when a person with an opioid dependency has abstained from using opioids for 12 to 24 hours and is in the early stages of opioid withdrawal**. It is important to note that buprenorphine can bring on acute withdrawal for patients who are not in the early stages of withdrawal and who have other opioids in their bloodstream.
- **The Stabilization Phase** begins after a patient has discontinued or greatly reduced their misuse of the problem drug, no longer has cravings, and experiences few, if any, side effects. The buprenorphine dose may need to be adjusted during this phase. **Because of the long-acting agent of buprenorphine, once patients have been stabilized, they can sometimes switch to alternate-day dosing instead of dosing every day**.
- **The Maintenance Phase** occurs when a patient is doing well on a steady dose of buprenorphine. The length of time of the maintenance phase is tailored to each patient and **could be indefinite**. Once an individual is stabilized, an alternative approach would be to go into a medically supervised withdrawal, which makes the transition from a physically dependent state smoother. People then can engage in further rehabilitation—with or without MAT—to prevent a possible relapse.

Naabt.org. Buprenorphine Education: Technical explanation (2018).

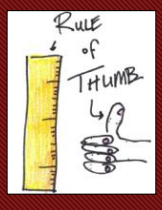
FAQ

"If someone is on buprenorphine for MAT and they have acute pain warranting opioids, should we stop the buprenorphine while giving opioids?"

As a rule of thumb, **buprenorphine should <u>not</u> be discontinued if a patient develops acute pain warranting opioids for management**.

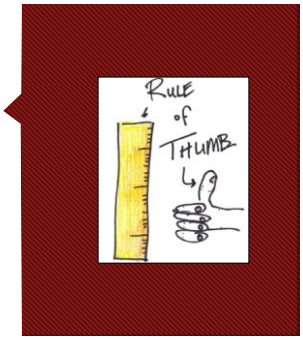
Buprenorphine should be continued during opioid therapy at the same dose prescribed by the outpatient prescriber.

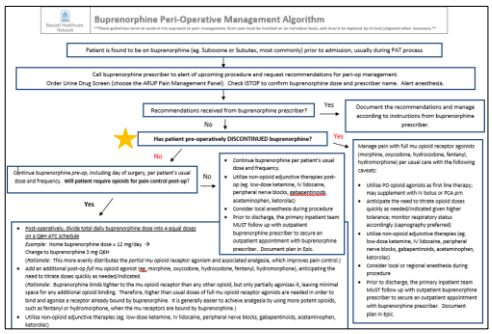
The outpatient buprenorphine prescriber should be contacted to confirm buprenorphine dose and to be alerted the patient will receive opioids for pain management.



For **peri-operative** surgical pain **management**, the **buprenorphine prescriber should be contacted in advance of surgery** to recommend buprenorphine discontinuation or continuation, and to confirm the dose.

If buprenorphine discontinuation is recommended, opioids should not be given any sooner than 24 hours, ideally 2-3 days, after last buprenorphine dose to minimize risk of overt opioid withdrawal.





Continue buprenorphine *pre-op*, including day of surgery, per patient's usual dose and frequency.

Will patient require opioids for pain control post-op?

Yes

Post-operatively, divide total daily buprenorphine dose into 4 equal doses on a Q6H ATC schedule
Example: Home buprenorphine dose = 12 mg/day → Change to buprenorphine 3 mg Q6H
(*Rationale:* This more evenly distributes the *partial* mu opioid receptor agonism and associated analgesia, which improves pain control).

Add an additional post-op *full* mu opioid agonist (eg. morphine, oxycodone, hydrocodone, fentanyl, hydromorphone), anticipating the need to titrate doses quickly as needed/indicated.
(*Rationale:* Buprenorphine binds tighter to the mu opioid receptor than any other opioid, but only partially agonizes it, leaving minimal space for any additional opioid binding. Therefore, higher than usual doses of full mu opioid receptor agonists are needed in order to bind and agonize a receptor already bound by buprenorphine. It is generally easier to achieve analgesia by using more potent opioids, such as fentanyl or hydromorphone, when the mu receptors are bound by buprenorphine.)

Utilize non-opioid adjunctive therapies (eg. low-dose ketamine, IV lidocaine, peripheral nerve blocks, gabapentinoids, acetaminophen, ketorolac).

Consider local or regional anesthesia during procedure.

Prior to discharge, the primary inpatient team MUST follow up with outpatient buprenorphine prescriber to secure an outpatient appointment with buprenorphine prescriber. Document plan in EMR.

Key Points

- Buprenorphine is a partial mu opioid receptor agonist FDA indicated for induction and maintenance of opioid dependence with a presumed ceiling effect on euphoria, and additional research warranted to evaluate ceiling effect in analgesia and respiratory depression
- Butrans, Belbuca, Subutex, and Buprenex are all available as pain management agents
- There is no agreed upon MME for buprenorphine
- In most cases, buprenorphine should be continued at the home dose during acute pain episodes warranting opioid therapy, and additional opioids initiated for acute pain
- Rapid uptitration of opioids may be necessary because buprenorphine is bound to the mu opioid receptor
- Evaluate patients on MAT using the same principles of pain assessment and non-opioid adjunctive therapy as you would in a patient not on MAT

References

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Questions?

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