Buprenorphine: Clinical Pearls for Safe & Effective Use

Amanda Engle, PharmD, BCPS
Assistant Professor, Albany College of Pharmacy and Health Sciences

Disclosures

- Dr. Engle has nothing to disclose

Objectives

- Define clinically relevant pharmacokinetic and pharmacodynamic principles of buprenorphine
- Contrast different buprenorphine formulations
- Synthesize an acute pain management plan for a patient on buprenorphine for medication assisted therapy (MAT) utilizing best practice analgesia strategies in this special population
What is Buprenorphine

FDA Labeled Indication
- For induction and maintenance treatment of opioid dependence
- Prescription required; 200 waives to obtain DEA II license number
- www.samhsa.gov/medication-assisted-treatment/buprenorphine-waiver-management

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
Medication Assisted Therapy (MAT), particularly with opioid agonist medications (e.g., 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.

What is Buprenorphine

“Medication Assisted Therapy (MAT), particularly with opioid agonist medications (e.g., 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.”

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.”
What is buprenorphine

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

What is Buprenorphine?

Single agent (buprenorphine only) formulations:
- Subutex sublingual tablet MAT
- Probuphine intradermal implant MAT
- Sublocade subcutaneous injection MAT
- Butrans transdermal patch chronic pain
- Belbuca buccal film chronic pain
- Buprenex injectable solution acute pain
What is Buprenorphine

Combination Formulations
- Bunavail (buprenorphine and naloxone) buccal film  MAT
- Suboxone (buprenorphine and naloxone) film  MAT
- Zubsolv (buprenorphine and naloxone) sublingual tablets  MAT

What is Buprenorphine?

Exhibit 1. Buprenorphine Products for Treatment of Opioid Use Disorder

What is buprenorphine
What is buprenorphine

- **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 tailor-made for 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.

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### FAQ

**“I heard it said that if someone is on buprenorphine for addiction "by law" you have to keep them on the same dose they came in on, is that true?”**

**Yes.**

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**Recommended daily dose for maintenance:** 16 mg bup / 4 mg nalox

**Range of 4 mg/1 mg buprenorphine/naloxone to 24 mg/6 mg buprenorphine/naloxone per day**

Doses should be incrementally adjusted to a level that holds the patient in treatment and suppresses opioid withdrawal effects.
Clinically Relevant Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

- Absorption
  - Not absorbed entirely due to significant first pass metabolism
  - Highly lipophilic
  - Well absorbed by oral mucosa

- Bioavailability
  - % Tablet: 31%
    - Zubsolv 5/1.4 mg vs other SL tablet 8/2 mg
  - % 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

Pharmacokinetics

- Metabolism
  - Hepatic
    - Avoid use in severe liver disease

- Mean Elimination Half-Life
  - 24 – 48 hours
    - slow dissociation from mu receptors prolongs effective half life
Pharmacodynamics

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


Clinically Relevant Pharmacodynamics
Pharmacodynamics

- Common Side Effects at Therapeutic Doses
  - Headache
  - Dry mouth
  - Constipation
Pharmacodynamics

- 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, goosebumps, dilated pupils in normal light, diarrhea, cramps, insomnia, nausea, anxiety, depression, dehydration, cravings

Pharmacodynamics

- Precautions
  - Increased risk of CNS and respiratory depression with concurrent use of opioid analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics, or other CNS depressants (including alcohol)
  - Abuse Potential
  - Dependence
  - Hepatitis/Hepatic Impairment
  - Use in opioid naive patients
  - Orthostatic Hypotension
  - Increased CSF Pressure
  - Use in opioid naive patients

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PK/PD

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.
What is Buprenorphine

“Does buprenorphine withdrawal look the same clinically as other opioids?”

Yes.

Yes, buprenorphine withdrawal presents the same clinically as other opioids. Consider using the Clinical or Objective Opioid Withdrawal Scale (COWS or OOWS) to monitor symptoms and treat accordingly.

Clinically Relevant Drug Interactions

Drug-Drug Interactions

- Benzodiazepines & other Sedatives
- Alchol
- Opioid Antagonists
- Naltrexone
- Opioid Agonists
What is Buprenorphine

*Can you overdose on buprenorphine?*

Yes. It is possible to overdose on buprenorphine. Patients are at higher risk for overdosing on buprenorphine when on other respiratory depressive medications, particularly benzodiazepines. Treating buprenorphine overdose with naloxone is more difficult than other opioid overdoses because of how tightly bound buprenorphine is to the mu receptors. Significantly larger naloxone doses are usually required.
Pain Management in Concurrent Buprenorphine Therapy

Buprenorphine in Pain Management

- Analgesics
  - Butrans
  - Belbucca
  - Buprenex

Medication Assisted Treatments
- Subbuteo (buprenorphine/naloxone) SL film
- 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

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 not 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 buprenorphine prescriber.

The outpatient buprenorphine prescriber should be contacted to confirm buprenorphine dose and to alert the patient will be receiving 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.
Benefits:
- Long half-life → long acting opioid → chronic pain
- Ceiling Effect: Respiratory Depression, Euphoria
- Concurrent addiction with chronic pain
- Do NOT need DATA 2000 waiver for pain indication
- Abuse deterrent formulation (buprenorphine as a single agent formulation is not)

Drawbacks:
- Long half-life → long acting opioid → chronic pain
- Ceiling Effect: Analgesia
- Highest mu receptor binding affinity of all opioids
- Naloxone reversal requires significantly higher doses
- Difficult acute pain treatment requiring significantly higher doses of other opioids
- Unknown equianalgesic dose
- Data for acute pain management needed
- Still abused
- Stigma

"Can I use suboxone for pain?"

Can I use suboxone for pain?

MAT: Medication Assisted Therapy
Case Study

- 52M adm for planned left hip replacement with PMH significant for Opioid Use Disorder on MAT (suboxone 8 mg/2 mg BID) and severe OA of left hip on daily ibuprofen 400 mg po q6h ATC. The patient did not discontinue suboxone prior to surgery, but did hold his ibuprofen for a week pre-op.
- 20 year history of oxycodone abuse with last relapse 7 years ago. Suboxone prescriber reported pt has been doing very well with a stable family, job, excellent compliance to clinic appointments and no dirty urine drug screens since suboxone therapy began 7 years ago.
- The patient is now in the PACU immediately post-op.
MAT: Medication Assisted Therapy
Case Study

Which of the following is the best post-operative suboxone management strategy?

1. Call the suboxone prescriber for acute pain recommendations
2. Resume the usual total daily dose of suboxone (16 mg), but split the daily dose into 4 divided doses (suboxone 4 mg SL q6h ATC)
3. Discontinue suboxone and initiate usual opioids for post-hip replacement management
4. Increase home suboxone dose in anticipation of acute post-operative pain
5. Convert buprenorphine to morphine using equianalgesic table to calculate starting morphine dose

In addition to suboxone 4/1 mg SL q6h ATC, what else should we do for his post-op pain?

1. No additional analgesics are needed, since suboxone contains buprenorphine which is already an opioid and produces analgesia
2. Initiate oxycodone 5-10 mg po q4h prn pain and assess for adding non-opioid adjunctive therapy
3. Initiate morphine 7.5-15 mg po q4h prn pain and assess for adding non-opioid adjunctive therapy
4. Avoid opioids altogether in this patient with a history of drug addiction
Pain Management Checklist

1. Establish reasonable expectations for pain control
2. Identify source(s) and type(s) of pain
3. Determine what therapies the patient is using, what they have tried, and what has/has not worked in past
4. Identify significant comorbidities
5. Think about non-pharmacologic approaches and use of adjuvant therapies as appropriate
6. If using opioids, consider 24 hour OME prior to titrating dose, use morphine first, initiate constipation regimen, and assess need for continuous pulse ox
7. Discuss plan for pain management with patient

Comprehensive Pain Assessment

<table>
<thead>
<tr>
<th>NF</th>
<th>P</th>
<th>G</th>
<th>R</th>
<th>S</th>
<th>T</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Precipitating Factors</td>
<td>Quality</td>
<td>Radiation</td>
<td>Severity</td>
<td>Temporal factors</td>
<td>Associated factors</td>
</tr>
<tr>
<td>What makes the pain better?</td>
<td>What makes the pain worse?</td>
<td>Pain descriptors (burning, sharp, dull, aching, etc.)</td>
<td>Where is the pain?</td>
<td>How does this pain compare with other pain you have experienced?</td>
<td>Pain starts?</td>
<td>Does the intensity of the pain change with time?</td>
</tr>
</tbody>
</table>

Comprehensive Pain Assessment

Non-neurologic

- Mechanical
  - Compression
  - Mechanical

Neurologic

- Painful peripheral neuropathy
- Nerve root compression


definitions of pain patterns

- Nociceptive
  - Visceral pain

- Neuropathic
  - Neurogenic pain

- Inflammatory
  - Arthritis

- Musculoskeletal
  - Muscle, tendon, ligament pain

- Tissue Injury
  - Mechanical
  - Compression

- Painful peripheral neuropathy
- Nerve root compression
Key Points

- Buprenorphine is a partial mu opioid receptor agonist FDA indicated for induction and maintenance of opioid dependence with a ceiling effect on euphoria, analgesia, and respiratory depression.
- For MAT, there are many single agent (bup) and combination agent (bup/nal) available in varying formulations (SL film, SL tablet, buccal film, SC injection, intradermal implant).
- Concurrent use of buprenorphine with alcohol or benzodiazepines significantly increases risk of overdose and death.
- Buprenorphine may be continued during acute pain episodes warranting opioid therapy. Prescribe the usual amount of opioid required for average pain control and monitor closely, recognizing rapid titration 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

Questions?

Amanda Engle, PharmD, BCPS
Assistant Professor
Albany College of Pharmacy & Health Sciences
Amanda.Engle@acphs.edu