Buprenorphine & opioid use disorder

February 10, 2019 by Josh Farkas

Between 1999-2017, ~400,000 people died from opioid overdose. That’s over half the number of Americans who have ever died from HIV. This is currently the most urgent public health crisis in the United States.

It is increasingly clear that opioid use disorder (OUD) is a chronic psychological disease involving persistent changes in neurobiology. Abstinence programs have been shown to fail, because cravings persist for months after the physical symptoms of withdrawal abate. Thus, patients with OUD require ongoing medical and psychiatric care in the same manner as patients with severe depression. To resolve the opioid crisis, we must invite patients with OUD into the house of medicine and treat them compassionately and effectively.

Addiction medicine specialists are leading the charge against OUD, but that’s not enough. Patients with OUD interact with practitioners across the entire healthcare system (e.g. emergency physicians, intensivists, and hospitalists). Everyone managing these patients should be prepared to
treat this disorder. Ideally, therapeutic strategies for OUD should be integrated across healthcare networks (not merely addiction specialists often working in silos).

In critical care, we often focus on high-tech, invasive therapies. More mundane things may be overlooked. OUD is often overlooked because these patients generally won’t die from opioid intoxication within our walls. Furthermore, if an OUD patient goes home and overdoses, this will be blamed on the patient (whereas if a patient with coronary disease went home and died, we would feel responsible). The unfortunate truth is that OUD is a pervasive and lethal disease, deserving our respect as much coronary disease. The good news is that new therapies have improved the outlook in OUD, so ongoing efforts to treat can be very effective.

Recently, medication-assisted therapy with buprenorphine has emerged as a preferred therapy for OUD. Especially in rural areas, this may be the only logistically feasible strategy for providing medical therapy to these patients. Buprenorphine is supported by a strong evidence base demonstrating harm reduction and improved adherence to therapy.

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**buprenorphine basics**

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**understanding buprenorphine/naloxone combination products**

- Buprenorphine is typically delivered in sublingual strips or tablets which also contain naloxone.
- Naloxone isn’t absorbed, but is included merely to avoid tampering with the strips.
- For patients in the hospital under supervised treatment, it is equally effective to provide buprenorphine alone.
- The best way to think about these products is simply as a safe delivery device to provide the patient buprenorphine.

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**buprenorphine pharmacodynamics**

- Buprenorphine has a high affinity for the mu opioid receptor, but it is a partial agonist. This makes it a perfect drug to use for OUD:
  - a) If the patient takes heroin while on buprenorphine, the buprenorphine will tend to block the effect of heroin (thereby affording some protection against respiratory arrest).
  - b) If the patient takes an excessive dose of buprenorphine, they won’t have a respiratory arrest (buprenorphine is a partial agonist, giving it a ceiling effect).
- Buprenorphine is an antagonist of the kappa opioid receptor, which may give it anti-depressant properties.
buprenorphine pharmacokinetics

- Buprenorphine is generally provided as a sublingual film with peak serum levels 1-2 hours after administration. Its sublingual bioavailability is ~50%.
- Buprenorphine is cleared by the CYP3A4 enzyme system in the liver with a half-life of 24-60 hours.²
  - Drugs that interact with CYP3A4 may affect buprenorphine levels (table below).
  - Buprenorphine doesn’t seem to affect the levels of other medications.³
- Hepatic metabolism occurs via glucuronidation, which is fairly well preserved in cirrhosis.⁴
- Dose adjustment isn’t needed for renal dysfunction.⁵

### Drugs that can affect hepatic CYP3A levels & buprenorphine metabolism

<table>
<thead>
<tr>
<th>Inhibitors of CYP3A4 (increase buprenorphine levels)</th>
<th>Inducers of CYP3A4 (decrease buprenorphine levels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>Azole antifungals</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Diltiazem, verapamil</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Macrolides (clarithromycin &gt; azithromycin)</td>
<td>Pioglitazone, troglitazone</td>
</tr>
<tr>
<td>HIV protease inhibitors</td>
<td>Rifampin</td>
</tr>
</tbody>
</table>

### Safety

- Buprenorphine is a partial agonist, which by itself appears unable to cause respiratory arrest. Overall, buprenorphine is vastly safer than most other opioids (which are full-strength mu-agonists). For example, buprenorphine may be used intentionally to treat respiratory suppression induced by other opioids.
- Respiratory suppression may occur if buprenorphine is given in combination with other agents (e.g. benzodiazepines).

### Diversion/Abuse Potential

- Combined buprenorphine/naloxone seems to have a low abuse potential. For example, if it were dissolved and injected the naloxone would cause opioid withdrawal.

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https://emcrit.org/ibcc/buprenorphine/
Indications

- Buprenorphine/naloxone may be diverted to the street and sold illicitly. However, illicit buprenorphine/naloxone seems to be used to manage opioid withdrawal (rather than being used recreationally to get high). This illicit use of buprenorphine/naloxone isn’t necessarily bad. It’s safer for someone with OUD to use buprenorphine to avoid withdrawal, instead of using IV heroin or fentanyl.

**pregnancy**

- Ongoing OUD poses a huge risk to both mother and fetus.
- Buprenorphine is a preferred therapy for OUD throughout both pregnancy and breastfeeding. The MOTHER trial showed that buprenorphine use in pregnancy causes less neonatal abstinence syndrome compared to methadone.
- Pregnant and nursing women can be treated similarly to other women (AAEM White Paper 2020):
  - (1) Buprenorphine with naloxone is safe in pregnancy. Previous concerns regarding naloxone are unfounded.
  - (2) Buprenorphine should be continued during breastfeeding (drug transfer is minimal).

**buprenorphine initiation**

Patients commonly present following drug intoxication (sometimes requiring intubation). Traditionally we would send these patients home following evaluation for suicidality. However, it’s becoming increasingly clear that these patients may also require screening and therapy for OUD. Simply returning a patient to the community to continue illicit opioid use isn’t providing meaningful treatment.

**Approach to intoxicated patient who recovers in ICU**

<table>
<thead>
<tr>
<th>Old paradigm</th>
<th>New paradigm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery from acute intoxication</td>
<td>Recovery from acute intoxication</td>
</tr>
<tr>
<td>? Suicidal</td>
<td>? Suicidal</td>
</tr>
<tr>
<td>Consider psych hospitalization</td>
<td>Consider starting buprenorphine</td>
</tr>
<tr>
<td>Discharge home</td>
<td>Discharge home</td>
</tr>
</tbody>
</table>

Both depression and opioid use disorder are severe, persistent psychiatric disorders which place the patient at immediate risk. They both require thorough screening and aggressive therapy.


**Indications** for treatment:

- Patient with OUD who is interested in treatment.
- Patient should be in withdrawal (or impending withdrawal).
Contraindications: The only absolute contraindication to buprenorphine use is allergy to buprenorphine. However, some issues may need to be resolved prior to initiation. In some situations, alternative approaches may be needed (e.g. admission for simultaneous management of multiple problems, methadone clinic, or expert consultation).

- Hepatic failure
- Methadone use (especially if patients are planning to return to methadone therapy)
- Other active neurologic problems (e.g. multifactorial delirium, simultaneous alcohol intoxication or alcohol withdrawal)
- Other active medical problems (e.g. pneumonia, respiratory failure)
- Severe polysubstance abuse: Buprenorphine could theoretically synergize with alcohol or benzodiazepines to increase the risk of respiratory suppression. However, this may be the lesser evil, compared to ongoing uncontrolled OUD.

**Timing of Buprenorphine Initiation**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset, Hours</th>
<th>Peak</th>
<th>Resolution, Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>4–48</td>
<td>96 h</td>
<td>14–21</td>
</tr>
<tr>
<td>Fentanyl (intravenous)</td>
<td>2–5</td>
<td>8–12 h</td>
<td>4–5</td>
</tr>
<tr>
<td>Heroin</td>
<td>6–12</td>
<td>24–72 h</td>
<td>7–10</td>
</tr>
<tr>
<td>Short-acting prescription opioids</td>
<td>6–12</td>
<td>24–72 h</td>
<td>7–10</td>
</tr>
<tr>
<td>Long-acting prescription opioids</td>
<td>12–36</td>
<td>2–5 days</td>
<td>10–14</td>
</tr>
<tr>
<td>Methadone</td>
<td>24–72</td>
<td>4–6 days</td>
<td>14–21</td>
</tr>
</tbody>
</table>


- Buprenorphine is a partial agonist
  - If buprenorphine is started while the patient still has a considerable amount of other opioids on board, it may precipitate opioid withdrawal.
  - If buprenorphine is started while the patient has some withdrawal symptoms, the buprenorphine will make the patient feel better.
- Buprenorphine initiation should be delayed until the patient is experiencing signs and symptoms of mild-moderate opioid withdrawal. This is generally defined using a COWS score above seven ([COWS score calculator at MDCalc](https://www.mdcalc.com/cows-score-opiate-withdrawal)). This should include at least one objective sign of opioid withdrawal. If it's unclear whether the patient is in withdrawal, watchful waiting should reveal this.
- Patients taking longer acting opioids are at greater risk of induced withdrawal. As a general rule of thumb (AAEM White Paper 2020):
  - Patients using short-acting opioids (e.g. heroin) should wait >8-12 hours since last use
  - Patients using extended-release opioids (e.g. oxycontin, MS-contin) should wait >24 hours since last use
  - Patients on methadone should wait >72 hours after last use

**Initiation: Day #1**
Buprenorphine & opioid use disorder - EMCrit Project

Buprenorphine can cause isolated nausea. This may simply be treated with ondansetron.

Rarely, buprenorphine may cause exacerbation of withdrawal symptoms. This suggests the presence of significant residual opioid. Optimal treatment here is controversial. The following options may be considered:

1. Additional buprenorphine may overcome residual opioids, causing improvement in withdrawal symptoms (up to 32 mg).
2. Buprenorphine therapy may be held to allow for residual opioid to dissipate. Additional doses may be provided after several hours.

In the interim, non-opioid therapies may be used to control symptoms, for example:

- Clonidine or midazolam for anxiety.
- Ondansetron or prochlorperazine for nausea/vomiting.
- Loperamide for diarrhea.
- Acetaminophen and NSAIDs for pain (if no renal dysfunction); low-dose ketamine for refractory pain.

Factors to consider when selecting initial buprenorphine dose

<table>
<thead>
<tr>
<th>Lower dose on day #1 (4-16 mg sublingual)</th>
<th>Higher dose on day #1 (24-32 mg sublingual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid History &amp; Response to Buprenorphine</td>
<td>Light user Symptoms respond rapidly to BUP</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Able to obtain &amp; fill prescription Next dose of BUP will be in 24 hours</td>
</tr>
<tr>
<td>Risk of over-sedation</td>
<td>Risk factors: Older patient with comorbidities Intercurrent EIOH/BZD use</td>
</tr>
</tbody>
</table>

Based on algorithm from ed-bridge.org

**What if buprenorphine causes clinical worsening?**

- Buprenorphine can cause isolated nausea. This may simply be treated with ondansetron.
- Rarely, buprenorphine may cause exacerbation of withdrawal symptoms. This suggests the presence of significant residual opioid. Optimal treatment here is controversial. The following options may be considered:
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**maintenance therapy**

- The initial maintenance dose is usually ~16 mg/day.
- For patients who required higher doses initially for symptomatic relief, a higher maintenance dose may be required.

**discharge prescription**

- Ideally follow-up should be arranged prior to discharge, but this may not always be possible (e.g. over weekends).
  - Buprenorphine treatment practitioners can be located [here](https://www.samhsa.gov/medication-assisted-treatment/physician-program-data/treatment-physician-locator).
  - The patient should ideally be discharged with enough buprenorphine to last until they can obtain outpatient follow-up. However, outpatient buprenorphine can be prescribed only by a provider with an X-waiver.
    - Usual prescription is for 16 mg sublingual buprenorphine/naloxone daily for 3-7 days until a follow-up appointment (if known).
  - If no providers are available with an X-waiver, an alternative approach is to gradually provide the patient with a large cumulative dose of buprenorphine in the hospital (e.g. 32 mg). Since buprenorphine has a *ceiling effect*, this won’t increase the physiologic effect of the drug. However, providing a large total dose of buprenorphine will extend the duration of drug effect (e.g. ~3 days). This may provide the patient with enough time to seek outpatient follow-up. If they are unable to obtain follow-up within this time, they may return to the hospital for additional buprenorphine.
  - Patients should be counseled to avoid combining buprenorphine with benzodiazepine or alcohol to avoid excessive sedation.
  - Patients should be advised to return to the emergency department if unable to establish outpatient treatment.

**home induction**

- This involves prescribing buprenorphine for a patient who isn’t in active withdrawal. When withdrawal starts, buprenorphine can be initiated in a similar fashion that would be used in the hospital (e.g. 1-4 mg then repeat PRN, followed by 16 mg daily).
- Home induction may be a more viable option for patients who are taking opioids with a longer half-life (e.g. extended-release oxycodone). Such patients may not withdraw for days after cessation of illicit opioids.
- The drawback of home induction is that a patient could be pushed into opioid withdrawal at home, without practitioners available to help manage the situation. The risk of induced withdrawal may be minimized by the following:
  - (1) Encourage the patient to wait until they have definite, unequivocal symptoms of withdrawal before starting the buprenorphine.
  - (2) Start at a lower dose (e.g. 1-2 mg). If this first dose causes the patient to feel worse then stop before going further (e.g. possibly wait several hours before taking another dose).
- An instruction sheet to print out for patients may be found [here](https://ed-bridge.org/home-start).

**buprenorphine induction via microdoses (micro-induction)**

**general concept of micro-induction**

- Most strategies for buprenorphine initiation involve cessation of full agonist use, waiting for opioid withdrawal, and then starting buprenorphine (as described in the above section). This has the advantages that it is supported by the most evidence and that it may be logistically easiest (especially for outpatients).
- An alternative strategy is micro-induction. This involves a *gradual* and *overlapping* transition from full agonist to buprenorphine. The advantage of micro-induction is that it doesn’t require going through a period of opioid withdrawal.
- Micro-induction might be a good option for patients with opioid use disorder who are admitted to the hospital for another problem. The dosing regimens involved with micro-induction can be a bit tricky, but this isn’t an issue for patients who are admitted to the hospital already. Evidence supporting micro-induction is extremely scanty (two retrospective case series), so this should be performed cautiously and with close monitoring (30387894, 27499655).
  - Despite the lack of evidence, given the extremely low doses of buprenorphine involved, this is likely to be safe – particularly within a monitored setting.

**nuts and bolts of micro-induction**

- (1) *Continue* full opioid agonist
  - Continue the patient on PRN doses of full agonist opioid *throughout* the micro-induction period.
If the patient is on scheduled doses of full agonist, these may be continued as well.

(2) Gradually increase the dose of buprenorphine, for example:

- Day #1: 0.25 mg buprenorphine four times daily (for a total of 1 mg)
- Day #2: 0.5 mg buprenorphine four times daily (for a total of 2 mg)
- Day #3: 1 mg buprenorphine four times daily (for a total of 4 mg)
- Day #4: 2 mg buprenorphine four times daily (for a total of 8 mg)
- Day #5: 4 mg buprenorphine four times daily (for a total of 16 mg)

Withdrawal symptoms may occur, but they should be mild. Since the doses of buprenorphine being used are gradually escalated, they shouldn't throw the patient into full withdrawal. Management of withdrawal symptoms may include the following:

- (a) Symptomatic treatments as needed (e.g. clonidine and/or anti-emetics PRN)
- (b) More gradual dose-escalation of buprenorphine (e.g. cease dose escalation until withdrawal symptoms subside).
- (c) PRN dosing of full opioid agonist (which should already be ordered).

Following completion of the above induction period, buprenorphine dosing may be consolidated into a once-daily dose (e.g. 16 mg QD) and full opioid agonist may be discontinued. Alternatively, if buprenorphine is being used for pain management, a split-dosing strategy may be continued (e.g. 8 mg BID).


Acute pain management in a patient on chronic buprenorphine

With increasing success of buprenorphine in OUD, we will be seeing more patients on chronic buprenorphine who are admitted for an unrelated issue. Generally, this is straightforward: just continue the buprenorphine. Any practitioner can prescribe buprenorphine to patients admitted to the hospital (an X-waiver is not required). However, buprenorphine therapy is more complicated if the patient is suffering from acute pain.

**General principles**

Buprenorphine is an effective analgesic, with potency roughly thirty times higher than morphine. There is a ceiling effect on respiratory suppression and euphoric effects, but no ceiling effect on analgesia. These properties make buprenorphine an effective and safe analgesic.

Buprenorphine is generally conceptualized as a partial agonist, but as an analgesic it appears to be as effective as full agonists.

Buprenorphine has a higher affinity for the mu opioid receptor than other opioids. Therefore, buprenorphine could block the ability to use other opioids for breakthrough pain. However, this seems to occur only at higher doses of buprenorphine (>8-12 mg daily sublingual dose). At lower buprenorphine doses, there may be synergistic analgesia between buprenorphine and other opioids. Thus, there is no reason to completely stop buprenorphine. Current opinion favors continuation of buprenorphine (either at full or reduced dose).

All available studies of perioperative pain management in patients on buprenorphine focus on pain control. There is no data regarding potential effects on exacerbation of OUD. However, in general it has been shown that abrupt discontinuation of buprenorphine leads to high risk of recrudescent OUD. Therefore, discontinuation of buprenorphine should be avoided.

**Non-opioid analgesia**

- The cornerstone of any pain management strategy is non-opioid analgesia. For the patient on chronic buprenorphine, this is even more crucial. These patients have opioid tolerance, so opioid analgesia will inevitably be less effective.
- A multimodal approach combining several non-opioid medications is the most effective.
- Local measures may be helpful (e.g. nerve blocks or lidocaine patches).
- Scheduled acetaminophen (e.g. 1 gram orally q6hr) should be used, unless contraindicated.
- A pain-dose ketamine infusion (e.g. 0.15-0.3 mg/kg/hr) augments analgesia, with a minimal side-effect profile.
- Oral clonidine or IV dexmedetomidine will provide analgesia, while synergizing with ketamine (more on keta-dex here).
- Gabapentin may be beneficial (although there is less evidence regarding gabapentin use among critically ill patients).
- NSAIDs may be used in patients with low risk of acute kidney injury.

**Opioid management strategy for mild/moderate pain**

https://emcrit.org/ibcc/buprenorphine/
Basic measures

- Continue the same total daily dose of buprenorphine that the patient chronically takes. However, for analgesic efficacy, buprenorphine should be given more frequently. Thus, the patient's usual daily dose should be divided and given q6hr-q8hr.
- When combined with aggressive non-opioid analgesia, this should be adequate for mild/moderate pain (e.g. most patients in a medical ICU).

- If these aren't sufficient, two different options exist:
  - (a) Divided daily dose of buprenorphine may be augmented with additional PRN buprenorphine (e.g. 2-8 mg sublingual every 1-2 hours PRN). This may be preferable to the addition of full agonists, option (b) below (AAEM White Paper 2020).
  - (b) Breakthrough pain may be treated with full opioid agonists (e.g. morphine, fentanyl). Higher doses than usual will be required. With a sufficiently aggressive regimen of non-opioid analgesics, hopefully this won't be necessary.

Opioid management strategy for severe pain

- If the patient is on >12 mg buprenorphine daily, consider reducing the daily dose to 8-12 mg. This should be provided in divided doses q6hr-q8hr.
  - Consider adding a full opioid agonist (e.g. morphine) in a scheduled fashion to replace the missing buprenorphine.
  - Additional doses of full mu opioid agonist may be needed to control breakthrough pain.
  - When pain is resolving, taper off full opioid agonists and increase back to prior maintenance dose of buprenorphine.
  - Consider consulting anesthesia/pain specialists in situations of severe pain that require a reduction in buprenorphine dose.
Going further:

FREE MAT Waiver Training Online [here](https://learning.pccasnow.org/p/onlinematwaiver). This runs off of an iPhone, so you can get waivered while working out, or on the couch.


Institutional guidelines
- Yale: [ED-initiated Buprenorphine](https://medicine.yale.edu/edbup/)
- Vermont [buprenorphine practice guidelines](http://contentmanager.med.uvm.edu/docs/default-source/vchip-documents/vchip_2buprenorphine_guidelines.pdf?sfvrsn=2)
- [Ed-bridge.org](https://ed-bridge.org/)

Podcasts
- EM:RAP has a free, absolutely epic podcast with Rubin Strayer [here](https://www.emrap.org/episode/emrap2018/strayerisms).
- FOAMcast (by Lauren Westafer and Jeremy Faust) has a great podcast on this [here](https://foamcast.org/2018/11/20/medicated-assisted-therapy/)

Blogs & articles
- Buprenorphine: Where do we stand? [here](http://www.emdocs.net/buprenorphine-where-do-we-stand/). (David Cisewski, emDocs)

References

8. Duber H, Barata I, Ciòè-Peña E, et al. Identification, Management, and Transition of Care for Patients With Opioid Use Disorder in the...


The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.