Managing Acute and Perioperative Pain in Patients on Medication-Assisted Treatments (MAT) - Andrea Rubinstein, MD

March 24th, 2017

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Disclosure

- I have nothing to disclose
Objectives

- Be more confident addressing acute pain in patients on buprenorphine products for opioid use disorder and for patients on naltrexone formulations.
- Be able to list three important implications of chronic methadone use during the perioperative period.
- Understand the evidence-base for how to approach perioperative pain in patients on buprenorphine.

Which form of MAT is the easiest to manage preoperatively?

- A. Naltrexone
- B. Methadone
- C. Buprenorphine
Nuance

Noun: (n(y)oʊˈɑnəs) a subtle difference in meaning or opinion or attitude

The bottom line

Whenever possible, always continue MAT except sometimes if it is naloxone or naltrexone
Why Would You Want to Continue MAT?
Because stopping may put recovery at risk

Preparation vs. Perspiration

Perspiration

Preparation
My preparation

- Have a plan and a back-up plan
- Pre-op visit with patient with written instructions
- Discussion with the surgeon
- Email or discussion with the anesthesiologist
- Note in the chart to hospitalist about the recommendations
- Who to call in case of issues
- Check in post op day 1 and post op day 3
- If MAT is stopped, close contact and a plan for restart
Naltrexone/Naloxone

Naltrexone

- Opioid antagonist
- 50 mg tablets daily
- 380 mg injected IM every 4 weeks
- Binds competitively but does not activate mu receptor
- Blocks opioid analgesia
- Competitive block changes over time
Naltrexone

- Best strategy: schedule surgery at the end of cycle if using IM
- Wait 24 hours if using oral tablets
- Opioid tolerant vs. increased opioid sensitivity
- Restart naltrexone once abstinence from postoperative opioids is adequate
- Always try to utilize multi-modal opioid sparing analgesia strategies
- Discuss with perioperative team what experience and options are available
- Consider medic-alert bracelet
- Consider pre-op urine toxicology for non opioids (cocaine, meth etc.)

Digression: Multi-modal Analgesia

- Ketamine (single dose vs infusion)
- Regional anesthesia
- Neuraxial analgesia spinal/ epidural
- NSAIDS
- Acetaminophen
- Membrane stabilizers
- Lidocaine infusion
- Alpha 2 agonists (dexmedetomidine, clonidine)
Acute Pain and Naltrexone/Naloxone

- Non-steroidal anti inflammatory medications
- Acetaminophen
- Steroids
- Topical local anesthetics
- Management of expectations
- Consult with pain team

Sticky Situations: Naltrexone/Naloxone

- What if this is not enough?
- Emergency surgery?
- Perioperative team is unaware/unfamiliar with MAT
- Extended NPO time
Which drugs prolong QT intervals

- A. Ciprofloxacin
- B. Fluoxetine
- C. Promethazine
- D. Sevoflurane
- E. All of the above

Methadone
methadone

**The Fortunate**
- Inexpensive
- Intrinsically long-acting for withdrawal
- High oral bioavailability
- No significant toxic metabolites
- No accumulation in renal disease
- NMDA antagonist
- Liquid or pill form
- Easy dose adjustments
- Relatively low street value (liquid)

**The Unfortunate**
- Highly variable metabolism related
- Unpredictable half-life
- Unpredictable equi-analgesic potency
- Variable protein binding
- Genetic difference affect metabolism
- QT prolonging
- Multiple drug-drug interactions
- Conversion is not bi-directional
- Sleep apnea

**Bottom line:**
- Methadone used for MAT maintained up to surgery and throughout perioperative period
- Other opioids added on top for new acute pain and tapered off as tolerated
If only it were that simple…

- Methadone affects QT interval
- Addition or discontinuation of other drugs can alter serum levels and therefore risk
- Some patients on take home methadone may not be using the prescribed dose
- Methadone doses are not easy to determine
- Ask about previous analgesic strategies that worked
- Low pain threshold and low high pain experience
- The methadone for MAT will not be analgesic post op

Preoperative anesthesia/pain service consult
Continue methadone up to and including day of surgery
Pre operative EKG
(advise patients to bring their own methadone to the hospital)*

Minor procedure
Ambulatory Surgery
Resume regular dose immediately after surgery
Multi modal analgesia
Opioids as necessary
QT prolonging Abx?

Inpatient Surgery
While NPO give equipotent other opioid and additional opioids for pain control
Multimodal analgesia
Pre-op EKG & urine
Close monitoring when drugs/doses change

Major inpatient
debit and additional opioid for analgesia
Multi modal therapy
Ketamine
Watch for drug interactions
If off methadone for 5 days or more consider consult
Pre-op EKG and urine plus discussion with hospitalist
Pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy

<table>
<thead>
<tr>
<th></th>
<th>All Methadone</th>
<th>Methadone given</th>
<th>Methadone not given</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st 24 hour MSE</td>
<td>221.2 +/-138.2</td>
<td>202.0 +/-138.0</td>
<td>281 +/- 129.9</td>
</tr>
<tr>
<td>NSAID</td>
<td>44.8</td>
<td>36.4</td>
<td>71.4</td>
</tr>
<tr>
<td>Ketamine</td>
<td>58.6</td>
<td>54.5</td>
<td>71.4</td>
</tr>
<tr>
<td>Days APS</td>
<td>5.1 +/-3.4</td>
<td>4.0 +/-2/5</td>
<td>8.7 +/-3.4</td>
</tr>
</tbody>
</table>
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Acute Pain Methadone

- Other analgesics, including opioids can be used with methadone (watch metabolism and QT)
- Close monitoring if using opioids for acute pain
- 3 day quantity of other opioid is usually enough post-op

Sticky Situations: Methadone

- What if this is not enough?
- What if this is emergency surgery?
- What if the perioperative team is unaware of the MAT
- What if the patient is NPO

Mostly issue is changing other drugs changes methadone
Monitoring QT intervals

Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>IC50 for hERG Block</th>
<th>Maximum Plasma Conc. (Cmax)</th>
<th>Ratio IC50/Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAAM</td>
<td>2.2 μM</td>
<td>1.0 μM</td>
<td>2.2</td>
</tr>
<tr>
<td>Methadone</td>
<td>9.8 μM</td>
<td>3.6 μM</td>
<td>2.7</td>
</tr>
<tr>
<td>Meperidine</td>
<td>75 μM</td>
<td>1.3 μM</td>
<td>58</td>
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<tr>
<td>Fentanyl</td>
<td>1.8 μM</td>
<td>30 nM</td>
<td>60</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>7.5 μM</td>
<td>36 nM</td>
<td>208</td>
</tr>
<tr>
<td>Morphine</td>
<td>&gt;1 mM</td>
<td>2.5 μM</td>
<td>&gt;400</td>
</tr>
<tr>
<td>Codeine</td>
<td>&gt;300 μM</td>
<td>0.66 μM</td>
<td>&gt;455</td>
</tr>
</tbody>
</table>

From Katchman et al. [31].

hERG = human ether-a-go-go-related gene; LAAM = L-α-acetyl-methadol; conc. = concentration.
It ain't what you don't know, it's what you know for sure that just ain't so

Attributed to Mark Twain…
Buprenorphine/naloxone can best be described as an agonist-antagonist because

- A. Buprenorphine is the agonist and naloxone is the antagonist
- B. Buprenorphine is an agonist at mu and an antagonist at kappa
- C. Buprenorphine is an agonist up to a certain dose and then it becomes an antagonist
- D. Buprenorphine is an agonist but it is an antagonist for other opioids

What we’re sure we know (that just ain’t so)

- It isn’t (a very good) analgesic
- It has a ceiling effect for analgesia
- It blocks other opioids
**Concept #1: Analgesia**

*Journal of Clinical Pharmacy and Therapeutics*

Commentary

The clinical analgesic efficacy of buprenorphine

R. B. Raffa* PhD, M. Tkalczyk* PharmD, H.-M. Huang* PharmD, K. Kallman* PharmD, D. E. Luckeinstein* PharmD, H. Chen* PharmD, M. J. Shapiro† PharmD, O. A. Novotan† PharmD, J. K. Tian† PharmD and J. V. Pogulis‡†‡†† MD

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**Ceiling Effect**

Dose-Response Curves for Three Opioid Painkillers:

- **Hi**
- **Lo**

Drugs:
- Fentanyl
- Buprenorphine
- Heroin

Effects:
- Total apnea (fatal overdose)
- Powerful hospital pain relief
- One normal Vicodin tablet

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Which of the following statements are true?

- A. In a patient on buprenorphine taking another opioid can precipitate withdrawal
- B. In a patient on buprenorphine taking another opioid will not offer additional analgesia
- C. In a patient on morphine buprenorphine can precipitate withdrawal
- D. All of the above

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Concept: Opioid Blocking

“While patients are taking opioid pain medications, the administration of buprenorphine generally should be discontinued. Note that until buprenorphine clears the body, it may be difficult to achieve analgesia with short-acting opioids.”

Apparently the government does not need to use footnotes to reference where their information comes from....
Pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy

<table>
<thead>
<tr>
<th></th>
<th>All Buprenorphine</th>
<th>Buprenorphine Given</th>
<th>Buprenorphine NOT given</th>
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</thead>
<tbody>
<tr>
<td>1st 24 hour MSE</td>
<td>200 +/-128.8</td>
<td>155.2 +/-135.5</td>
<td>245.5 +/- 109.3</td>
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<tr>
<td>NSAID</td>
<td>31.8</td>
<td>18.2</td>
<td>45.5</td>
</tr>
<tr>
<td>Ketamine</td>
<td>63.6</td>
<td>27.3</td>
<td>100</td>
</tr>
<tr>
<td>Days APS</td>
<td>4.5 +/-0.3</td>
<td>3.0 +/-1.7</td>
<td>5.9 +/- 0.9</td>
</tr>
</tbody>
</table>

And what about naloxone…..

- Naloxone in buprenorphine is not bio-available unless injected
- It does not block other opioids when used as directed
- It is not the cause of precipitated withdrawal when taken sublingually.
Algorithm for managing perioperative buprenorphine

Continue buprenorphine up to and including day of surgery
Communication with Surgeon and Anesthesia as well as hospitalist

Minor procedure or ambulatory surgery
Resume buprenorphine at next dose
use multimodal analgesia
use additional buprenorphine or secondary opioid if necessary
Follow up by phone on post op day 1 and 3

Moderate inpatient surgery
Continue buprenorphine
multi-modal analgesia
high affinity short acting high affinity opioids if necessary

Major surgery NPO x >48 hours
Continue Buprenorphine IV or dissolving strips
Supplemental high affinity opioids as needed
Multimodal analgesia

Acute Pain: Buprenorphine

- No problem with adding any appropriate drug, including opioids to a buprenorphine regimen
- Some patients can be managed with increased doses of buprenorphine in perioperative period (QID)
- Close monitoring if using opioids for acute pain
- 3 day quantity of additional opioid is usually enough
Sticky Situations: Buprenorphine

- What if this is not enough?
- What if this is emergency surgery?
- What if the perioperative team is unaware of the MAT
- What if the patient is NPO

Sometimes the problem is not the drug...buprenorphine was restarted after a 4 day abstinence while other opioids were being given....

Buprenorphine Maintenance Therapy Hinders Acute Pain Management in Trauma

COLIN J. HARRINGTON, M.D.,* VICTOR ZAYDULIF, M.D., M.P.H.†

From the *Departments of Psychiatry and Medicine, Brown Medical School and Rhode Island Hospital, Providence, Rhode Island and the †Department of Surgery, Vanderbilt University Medical Center, Nashville, Tennessee

The patient’s agitation and complaints of pain persisted. Agitation was managed with haloperidol and lorazepam. Pain was treated with high dose full agonist opiates. By postinjury day (PID) 3, the patient's analgesic needs began to decline. Additional history revealed that the patient was active in a buprenorphine maintenance program. His preadmission buprenorphine maintenance regimen of buprenorphine/naloxone (2 mg/0.5 mg) combination therapy was restarted on PID 4, with the aim of achieving better analgesia. Subsequent tapering of narcotics, however, was unsuccessful and the patient received 50 mg of morphine, 37 mg of haloperidol, 8 mg of lorazepam, and 17 mg of midazolam on PID 6.
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### Binding Affinity

Volpe, DA et al. Regulatory toxicology and pharmacology 2011; (59)3, 385-90

<table>
<thead>
<tr>
<th>Drug</th>
<th>$K_i$</th>
</tr>
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<tbody>
<tr>
<td>Sufentanil</td>
<td>0.136</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.27</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.36</td>
</tr>
<tr>
<td>Morphine</td>
<td>1.17</td>
</tr>
</tbody>
</table>

### Summary

- Most MAT can be maintained preoperatively with pre-planning
- Even with Pre-planning problems can arise that perioperative team may not be equipped to handle
- Each patient should be assessed for their particular MAT regimen, their surgery, their team and plans should be made accordingly
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References on Buprenorphine


References on Methadone


References on Naltrexone/Naloxone


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Tapering Chronic Opioids

Friday, 05/19/2017
Friday, 06/23/2017
Friday, 07/28/2017
Friday, 08/18/2017*
Friday, 09/22/2017

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OR
Free on the CHCF TAPC Program Resource Page at: https://tapcprogram.com/
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