Managing Pain in patients on MAT

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Disclosure

Dr. Weimer was a consultant to Indivior, for which she received honorarium. This was a one-time consultation to discuss how to stop taking medication they manufacture.

Many slides adapted and courtesy of Dr. Dan Alford at Boston University.
Learning Objectives

• Describe the management of severe pain in patients with a history of opioid use disorder maintained on medication assisted treatment

• Describe the management of post-op pain in patients with a history of opioid use disorder maintained on medication assisted treatment
Epidemiology

• 52% treatment seeking opioid-dependent veterans complained of moderate to severe chronic pain

• 37%-61% of MMT patients have chronic pain

• Pain plays substantial role in initiating and continuing illicit opioid use

Chronic Pain not Associated with Worse MAT Outcomes

• Prospective study of office-based buprenorphine treatment
• Comparing treatment retention and opioid use among participants with and without pain
• Among 82 participants, no association between pain and buprenorphine treatment outcomes

Altered Pain Experience

- In experimental pain studies...
  - Patients with active opioid use disorder have less pain tolerance than peers in remission or matched controls
  - Patients with a h/o opioid use disorder have less pain tolerance than siblings without an addiction history
  - Patients on opioid maintenance treatment (i.e. methadone, buprenorphine) have less pain tolerance than matched controls

- Methadone-maintained women had increased pain and required up to 70% more oxycodone equivalents after cesarean delivery

Born with decreased pain tolerance with higher risk of opioid addiction

Opioid addiction altered nervous system resulting in lower pain tolerance

“WHO WAS FIRST?”
Opioid Agonist Therapy
&
Acute Pain
General Principles
“Opioid Debt”

- Patients who are physically dependent on opioids (i.e. methadone or buprenorphine) must be maintained on daily equivalence before ANY analgesic effect is realized with opioids used to treat acute pain.
- Opioid analgesic requirements are often higher due to increased pain sensitivity and opioid cross tolerance.

Peng PW, Tumber PS, Gourlay D: Can J Anaesthesia 2005
Methadone Maintenance & Acute Pain
Compared 25 post-surgical MMT patients who had received opioid analgesics to 25 MMT patient controls matched for age, sex, duration on MMT.

After 20 month follow-up, no difference in relapse indicators such as substance use patterns and methadone dose changes.

Conclusion: Opioid analgesics may be used safely in MMT patients with acute post-surgical pain without compromising addiction treatment.

Kantor TG et al. Drug and Alc Dependence. 1980
Acute Pain
Methadone Maintenance Treatment (MMT)
Clinical Recommendations

- **Remember:** Methadone maintenance dosed every 24 hours does not confer analgesia beyond 6-8 hours
- Continue usual *verified* methadone dose from opioid treatment program
- Treat pain aggressively with conventional analgesics, including opioids at higher (1.5 times) doses and shorter intervals
- Avoid using mixed agonist/antagonist opioids (e.g., butorphanol (Stadol)) as they will precipitate acute withdrawal
- Consider adjuvant therapies such as nerve blocks, ketamine (NMDA antagonist), NSAIDs, acetaminophen

Methadone Maintenance & Chronic Pain
The good news...

- Analgesia (6-8 hrs) from methadone dose may be good test for opioid responsive pain
- Analgesia for 24 hrs is likely opioid withdrawal mediated pain
- Closely monitored in MMT e.g., drug testing, pill counts
- Methadone will block euphoric effects of opioid analgesics

The bad news...

- MMT programs only able to dose daily (some clinics will dispense “split doses”)
- It is illegal to prescribe methadone for the treatment of addiction outside an opioid treatment program
- Prescribed opioid analgesics may interfere with drug testing in MMT e.g., opiates and semisynthetics
- Opportunities at MMT to divert prescribed opioids
In an ideal world...

would be able to treat both opioid use disorder and chronic pain with methadone dosed TID or QID either in the MMT or in primary care with highly structure and monitoring

In reality...

Use adjuncts, emphasize non-opioid options
Buprenorphine Maintenance & Acute Pain
**Buprenorphine as an Analgesic**

- **Parenteral and transdermal formulations** approved for pain *not* opioid use disorder treatment
  - **CANNOT** be used off-label under Drug Addiction Treatment Act (DATA) of 2000

- **Sublingual formulation** approved for opioid use disorder *not* pain treatment
  - Can be used off-label
Buprenorphine as an Analgesic

- Small studies in Europe and Asia demonstrate analgesic efficacy of SL formulation (0.2-0.8 mg q 6-8 h) in opioid naïve post-operative pain

- CNS and respiratory depression ceiling effect

- Analgesic ceiling effect is UNCERTAIN
  - Differing data on analgesic ceiling effect in animal models
  - **No** published data indicating an analgesic ceiling in humans

Edge WG et al. Anaesthesia. 1979
In 20 healthy volunteers... Doubling dose increased peak analgesic effect by 3.5x while respiratory depression remained unchanged

Acute Pain
Buprenorphine Maintenance Treatment

Theoretical Concern

• Buprenorphine (a partial mu agonist) may
  • antagonize the effects of previously administered opioids or
  • block the effects of subsequent administered opioids

• However...Experimental mouse and rat pain models
  • Combination of buprenorphine and full opioid agonists (morphine, oxycodone, hydromorphone, fentanyl, etc) resulted in additive or synergistic effects
  • Receptor occupancy by buprenorphine does not appear to cause impairment of mu-opioid receptor accessibility

Englberger W et al. European J of Pharm. 2006
1. Continue buprenorphine and titrate short-acting opioid analgesic
2. D/c buprenorphine, use opioid analgesic, then re-induce
3. Divide buprenorphine to every 6-8 hours
4. Use supplemental doses of buprenorphine*
5. If inpatient,
   • d/c buprenorphine
   • start methadone 20-40mg (or other extended-release, long-acting opioid)
   • use short-acting, immediate-release opioid analgesics
   • then re-induce w/ buprenorphine when acute pain resolves

Alford DP. Handbook of Office-Based Buprenorphine Treatment of Opioid Dependence. 2010
Buprenorphine Maintenance & Perioperative Pain Management
Management of Sublingual Buprenorphine (Suboxone and Subutex) in the Acute Perioperative Setting

Elective Surgery

Surgical Team: Assess anticipated post-operative pain and opioid requirements

Minimal to no pain

- Ask the patient if they are still taking their buprenorphine

Still taking buprenorphine
- Surgeons ensure that the physician writing the buprenorphine is aware of surgery
- Continue the buprenorphine for post-op pain
- Do not prescribe supplemental opioids
- Consider adjuncts - Acetaminophen and/or NSAIDs

Off buprenorphine
- Access the amount of time since the last dose of buprenorphine
- If ≥ 5 days off buprenorphine, treat with traditional opioids
- Surgeons should contact the physician prescribing buprenorphine and ensure that they are aware of surgery
- After post-op pain normalizes, the patient may work with their physician to reinstate buprenorphine therapy

Moderate to severe pain

- Ask the patient if they are still taking their buprenorphine

Still taking buprenorphine
- Cancel surgery
- Patient return to the physician that prescribes their buprenorphine; coordinated by surgical team
- Should be taken off of buprenorphine and transitioned to short-acting opioids for ≥ 5 days prior to surgery by physician prescribing buprenorphine

Off buprenorphine
- Ensure ≥ 5 days off buprenorphine (otherwise cancel surgery - see above)
- Use traditional opioids for post-op pain; anticipate higher doses
- Consider adjuncts - acetaminophen, NSAIDs, gabapentin/pregabalin, low-dose ketamine infusion
- Consider regional anesthesia - preferably continuous catheters
- Anesthesiologists should consider alpha-2 agonists (clonidine or dexametomidine)
- Should return to physician writing their buprenorphine after normalization of post-op pain to reinstate buprenorphine therapy; coordinated by surgical team
• But this protocol...
  – Risks causing a disruption in the patient’s recovery from opioid use disorder by stopping buprenorphine during high anxiety preoperative period
  – Has never been evaluated and is based on a theoretical concern of pharmacological principles
• Take last buprenorphine dose on the morning of the day prior to the procedure
• Hold buprenorphine dose on day of surgery

• **Pre-procedure**: give single dose of ER/LA opioid (e.g., SR morphine 15 mg) on the day of procedure
Does it need to be so complicated?

Can it be as simple as managing acute pain in methadone maintained patients?
• 5 patients underwent 7 major surgeries (colectomy, knee replacement, small bowel resection, bilateral mastectomy)

• All maintained on stable doses of SL buprenorphine (2 mg – 24 mg) for chronic musculoskeletal pain – some with remote history of opioid use disorder

• By chart review, postoperative pain was adequately controlled using oral or IV full agonist opioids
• Observational study of peripartum acute pain management of buprenorphine (n=8) stabilized patients
  – Patients responded to additional opioid medication given for pain control
  *Jones HE et al. Am J Drug Alc Abuse 2009*

• DB RCT comparing IV patient-controlled analgesia (PCA) with buprenorphine and morphine alone and in combination for postoperative pain in adults undergoing abdominal surgery
  – In the combination group, buprenorphine did not appear to inhibit the analgesia provided by morphine
  *Oifa S et al. Clin Ther. 2009*

• Sub-analysis of the MOTHERS Study, no differences in pain management during delivery and the 1st three days postpartum for MM (n=21) and BM (n=19)
  *Hoflich AS et al. Eur J of Pain. 2011*
Acute Pain
Buprenorphine Maintenance Treatment
Accumulating Research

- Retrospective cohort of 1st 24 hours after surgery in 11 BM and 22 MM patients on patient controlled analgesia (PCA)
- No significant differences in pain scores, incidence of nausea, vomiting or sedation
- No significant differences in PCA morphine requirements

Authors conclude...

“results confirm that continuation of buprenorphine perioperatively is appropriate”

Macintyre PE et al. Anaesth Intensive Care 2013
• Dose buprenorphine BID or TID and/or increase overall dose
  – Usually do not exceed buprenorphine 24mg/day

• Option: add additional opioid **ON TOP** of buprenorphine
  – Choose opioid with high affinity for the mu receptor (hydromorphone or fentanyl)
  – Dose hydromorphone at higher dose to compete at the mu receptor
    • Example: Buprenorphine 24mg per day, add hydromorphone 4-6mg every 4-6 hours PRN

• Use scheduled adjuvant therapies (ketamine, nerve block, NSAID, Tylenol, gabapentin, SNRI, etc)

• Taper additional opioids after tissue healing
Buprenorphine Maintenance & Chronic Pain
Open-labeled study of 95 patients with chronic pain who failed long-term opioids and were converted to sublingual buprenorphine

- Mean buprenorphine dose 8mg/d (4-16mg) in divided doses
- Mean duration of treatment ~9 months
- 86% had moderate to substantial pain relief along with improved mood and function
- 6% discontinued therapy due to side effects or worsening pain

Chronic Pain
Buprenorphine Maintenance Treatment

- Systematic review
- 10 trials involving 1,190 patients
- Due to heterogeneity of studies, pooling results and meta-analysis not possible
- All studies reported effectiveness in treating chronic pain
- Majority of studies were observational and low quality
- Current evidence insufficient to determine effectiveness of SL buprenorphine for treatment of chronic pain

Cotes J, Montgomery L. Pain Medicine 2014
Naltrexone & Pain Management
Emergent Acute Pain

- Discontinue naltrexone
- Consult Anesthesia
- Opioid analgesics (high dose, IV fentanyl usually) administered under close observation
  - Naltrexone blockade can be overcome at 6-20x usual dose resulting in analgesia without significant respiratory depression or sedation
- Consider non-opioids and regional anesthesia
Naltrexone will block the effects of co-administered opioid analgesic

- **IM depot naltrexone**
  - peak plasma within 2-3 days, decline begins in 14 days
  - If possible, delay elective surgery for a month after last dose

- **Oral naltrexone**
  - Discontinue for at least 3 days prior to planned surgery

Vickers AP, Jolly A BMJ 2006