Managing Acute & Chronic Pain with Opioid Analgesics in Patients on Medication Assisted Treatment (MAT)

Daniel P. Alford, MD, MPH, FACP, DFASAM
Professor of Medicine
Assistant Dean, Continuing Medical Education
Director, Clinical Addiction Research and Education Unit
Boston University School of Medicine & Boston Medical Center
Daniel Alford, MD, has no financial relationships to disclose.

The contents of this activity may include discussion of off label or investigative drug uses. The faculty is aware that is their responsibility to disclose this information.
Target Audience

The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.
Educational Objectives

• At the conclusion of this activity participants should be able to:
  ▪ Describe the epidemiology of pain among individuals with opioid use disorder and factors that influence the overlap
  ▪ Contrast the key role of patient and provider perspectives on pain management
  ▪ Discuss general principles and different specific approaches for acute and chronic pain management in patients with opioid use disorder treated with methadone, buprenorphine, or naltrexone
Epidemiology

- 52% of treatment seeking veterans with opioid use disorder complained of moderate to severe chronic pain
- 37%-61% of patients taking methadone for opioid use disorder have chronic pain
- Pain plays a substantial role in initiating and continuing illicit opioid use

Substance Use and Chronic Pain

- Cross-sectional analysis of 589 adult patients who screened positive for any illicit drug use or prescription drug misuse, in an urban, hospital-based primary care practice
- Patients were asked about the use of substances to treat pain

<table>
<thead>
<tr>
<th>Substance Use</th>
<th>Percent Used for Chronic Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any illicit drug</td>
<td>51%</td>
</tr>
<tr>
<td>Marijuana use only</td>
<td>43%</td>
</tr>
<tr>
<td>Cocaine use only</td>
<td>42%</td>
</tr>
<tr>
<td>Heroin use only</td>
<td>71%</td>
</tr>
<tr>
<td>Prescription drug misuse</td>
<td>81%</td>
</tr>
</tbody>
</table>
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
- Conclusion: The presence of chronic pain in patients with opioid use disorder is not a barrier to successful opioid misuse treatment

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

1. Providers Fear Deception

Providers question the “legitimacy” of need for opioid analgesics (“drug seeking” patient vs. legitimate need)

“When the patient is always seeking, there is a sort of a tone, always complaining and always trying to get more. It’s that seeking behavior that puts you off, regardless of what’s going on, it just puts you off.”

-Junior Medical Resident
2. No Standard Approach

Patients perceive that the evaluation and treatment of pain and withdrawal is extremely variable among providers. This may be because there is no common approach nor are there clearly articulated standards.

“The last time, they took me to the operating room, put me to sleep, gave me pain meds, and I was in and out in two days. . . . This crew was hard! It’s like the Civil War. ‘He’s a trooper, get out the saw’. . .”

-Patient w/ Multiple Encounters

Pain and Addiction

Patient Perspective

3. Avoidance

Patients perceive that providers focus primarily on familiar acute medical problems and evade more uncertain areas of assessing or intervening in the underlying addiction problem—particularly issues of pain and withdrawal.

Patient/Resident Dialog
Resident: “Good Morning”
Patient: “I’m in terrible pain.”
Resident: “This is Dr. Attending, who will take care of you.”
Patient: “I’m in terrible pain.”
Attending: “We’re going to look at your foot.”
Patient: “I’m in terrible pain.”
Resident: “Did his dressing get changed?”
Patient: “Please don’t hurt me.”

4. Patient Fear of Mistreatment

Patients are fearful they will be punished for their drug use by poor medical care.

“I mentioned that I would need methadone, and I heard one of them chuckle. . .in a negative, condescending way. You’re very sensitive because you expect problems getting adequate pain management because you have a history of drug abuse. . .He showed me that he was actually in the opposite corner, across the ring from me.”

-Patient
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.

Methadone Maintenance & Acute Pain
Acute Pain
Methadone Maintenance Treatment (MMT)

- Methadone maintenance dosed every 24 hours does not confer analgesia beyond 6-8 hours
- Opioid analgesics will not cause excessive CNS or respiratory depression due to opioid cross-tolerance
- Risk of relapse to active drug use may be higher with inadequate pain management than with the use of opioid analgesics

Acute Pain

Methadone Maintenance Treatment (MMT)

- 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 substance use treatment.

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

- Continue usual *verified* methadone dose
- 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
- Careful use and monitoring of combination products containing acetaminophen

Methadone
Maintenance &
Chronic Pain
Chronic Pain
Methadone Maintenance Treatment (MMT)

The good news...

• Analgesia (6-8 hrs) from methadone dose may be good test for opioid responsive pain

• Analgesia for 24 hrs from methadone dose implies that pain 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 once daily (some clinics will dispense “split doses”)
- It is illegal to prescribe methadone for the treatment of substance use disorder
- Prescribed opioid analgesics may interfere with drug testing in MMT e.g., opiates and semisynthetics
- Opportunities at MMT to divert prescribed opioids
Chronic Pain
Methadone Maintenance Treatment (MMT)

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
Buprenorphine Maintenance & Acute Pain
# Buprenorphine Formulations

---

## FDA approval for OUD vs Pain

**For OUD** (can be used off label for pain)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>generic</td>
<td>2, 8 mg SL tabs</td>
<td>16 mg/d</td>
</tr>
<tr>
<td>Probuphine</td>
<td>74.2 mg SD implant</td>
<td>4 implants/6m</td>
</tr>
<tr>
<td>Buprenorphine/Naloxone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>generic</td>
<td>2/0.5, 8/2 mg SL tabs</td>
<td>16/4 mg/d</td>
</tr>
<tr>
<td>Bunavail</td>
<td>2.1/0.3, 4.2/0/7, 6.3/1 mg buccal film</td>
<td>8.4/1.4 mg/d</td>
</tr>
<tr>
<td>Suboxone</td>
<td>2/0.5, 4/1, 8/2, 12/3 mg SL film</td>
<td>16/4 mg/d</td>
</tr>
<tr>
<td>Zubsolv</td>
<td>1.4/0.36, 5.7/1.4 mg SL tab</td>
<td>11.4/2.8 mg/d</td>
</tr>
</tbody>
</table>

**For Pain** (cannot be used off label for OUD under DATA 2000)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belbuca</td>
<td>Buccal q12h</td>
</tr>
<tr>
<td>Butrans</td>
<td>Transdermal 7-day patch</td>
</tr>
<tr>
<td>Buprenex</td>
<td>IM/IV q6h</td>
</tr>
</tbody>
</table>
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

Buprenorphine as an Analgesic

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
  - block the effects of subsequently administered opioids

- However…Experimental mouse and rat pain models
  - Combination of buprenorphine and full opioid agonists (morphine, oxycodone, hydromorphone, fentanyl) 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
• 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 addiction

• By chart review, postoperative pain was adequately controlled using oral or IV full agonist opioids
Acute Pain
Buprenorphine Maintenance Treatment
Accumulating Research

- 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)

- Double-blind 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)
Acute Pain
Buprenorphine Maintenance Treatment
Accumulating Research

• Cohort of peripartum acute pain management of buprenorphine maintained (BM) patients (n=63) (44 vaginal deliveries, 19 C-section) matched retrospectively with controls
  ▪ BM patients had similar intrapartum pain and analgesia BUT experienced more postpartum pain requiring 47% more opioids following C-section (Meyer M et al. Eur J Pain. 2010)

• Sub-analysis of the MOTHER study, no differences in pain management during delivery and the 1st three days postpartum for MMT (n=21) and BM (n=19) (Hoflich AS et al. Eur J of Pain 2011)
Comparison of Post-Cesarean Opioid Analgesic Requirements in Methadone and Buprenorphine Maintained Women

• Retrospective cohort of 140 women on methadone and 55 on buprenorphine maintenance undergoing cesarean section

• Results
  • There were no differences in opioid requirements intraoperatively
  • Those in the buprenorphine group required less opioids preoperative and in the first 24 hours postpartum
  • There were no differences in postoperative complications between the two groups or length of hospitalization

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
Total Joint Arthroplasty in Patients Taking MAT Preoperatively

- Prospective matched cohort study of 17 patients on MAT (buprenorphine/naloxone or methadone) preoperatively

- Patients on MAT had:
  - Significantly more referrals to the pain service
    - 9 patients on MAT were referred to the pain service for intractable pain vs 1 patient in the control group
  - Significantly higher doses of opioids
    - 8x higher opioid doses vs patients in the control group
  - No significant difference with respect to length of stay, functional outcomes, and complications

Buprenorphine Maintenance Treatment

Clinical Recommendation

• Preclinical and clinical studies now suggest that concurrent use of opioid analgesics in patients maintained on buprenorphine is effective\(^1\)

• Recommendation for managing acute pain if opioid analgesics are needed is to:
  • Continue buprenorphine but in divided doses (every 8 hours) to take advantage of its analgesic properties and
  • Titrate short-acting opioid analgesic for additional pain management

\(^1\)van Niel JC et al. Drug Research, 2016
Buprenorphine Maintenance & Chronic Pain
Open-label 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 is insufficient to determine effectiveness of SL buprenorphine for treatment of chronic pain

Cotes J, Montgomery L. Pain Medicine 2014
Naltrexone
Maintenance &
Pain Management
Oral Naltrexone Blockade

“Time-action of naltrexone in detoxified ex-opiate addicts using 25 mg IV heroin challenges after naltrexone 100 mg dose”

Percent Blockade

<table>
<thead>
<tr>
<th>Time</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hours</td>
<td>96%</td>
</tr>
<tr>
<td>48 hours</td>
<td>87%</td>
</tr>
<tr>
<td>72 hours</td>
<td>47%</td>
</tr>
</tbody>
</table>

Acute Pain
Overcoming Naltrexone Blockade

- Hot plate test after XR-NXT or placebo, rats treated with opioid agonist (morphine, fentanyl, hydrocodone)
- Naltrexone blocks analgesic effects of opioids at conventional doses
- Naltrexone blockade can be overcome at 6-20x usual dose resulting in analgesia without significant respiratory depression or sedation

Dean RL et al. Pharmacol Biochem Behav 2008
Emergent Acute Pain and Naltrexone Management

• Discontinue naltrexone
• Consult Anesthesia
  ▪ Need to have healthcare providers specifically trained in the use of anesthetic drugs and management of respiratory effects of potent opioids
• Opioid analgesics (high dose) administered under close observation
  ▪ Need setting that is equipped and staffed for cardiopulmonary resuscitation
  ▪ Need to prepared to establish and maintain a patient airway with assisted ventilation if needed
• Consider nonopioids and regional anesthesia

For more information on injectable naltrexone and pain management, call 1-888-235-8008 or visit Vivtrolsafety.com
Perioperative Pain Management

- Naltrexone will block the effects of co-administered opioid analgesic
  - **PO naltrexone**
    - $t_{1/2}$ is 14 hours, d/c for at least 72 hrs preoperatively
    - 50% of blockade effect is gone after 72 hrs
  - **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

Vickers AP, Jolly A BMJ2006
Percent of Pain-related Post-Marketing AE Reports

- 0.79% Percentage post-marketing reports related to inadequate pain management
- 99.2% Percentage post-marketing reports not related to inadequate pain management

N=1,887

*Early P et al. Acute Pain Episode Outcomes in Patients Treated with Injectable Extended-Release Naltrexone (XR-NTX) presented as poster at ASAM 2013 annual meeting*

*Study funded by Alkermes*
Health Economics Retrospective Analyses

• Hypothesis: Frequent acute pain episodes that cannot be managed on an outpatient basis could elevate ER & hospital utilization rates
• Studies: All (4) published national commercial insurance database analyses
• Limitation: Studies were not RCTs; all used statistical case-mix cohort adjustment.
• Aggregate XR-NTX-treated population: N=1,323 patients
• Compared to all approved alcohol or opioid use disorder oral agents
• XR-NTX patients had:
  ▪ No greater ER use;
  ▪ Significantly and substantially fewer hospital admissions

Early P et al. Acute Pain Episode Outcomes in Patients Treated with Injectable Extended-Release Naltrexone (XR-TX) presented as poster at ASAM 2013 annual meeting Study funded by Alkermes
References

References

PCSS-MAT Listserv

Have a clinical question? Please click the box below!
PCSS-MAT Mentoring Program

- PCSS-MAT Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid addiction.

- PCSS-MAT Mentors comprise a national network of trained providers with expertise in medication-assisted treatment, addictions and clinical education.

- Our 3-tiered mentoring approach allows every mentor/mentee relationship to be unique and catered to the specific needs of both parties.

- The mentoring program is available, at no cost to providers.

For more information on requesting or becoming a mentor visit: pcssmat.org/mentoring
**PCSS-MAT** is a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with the: Addiction Technology Transfer Center (ATTC); American Academy of Family Physicians (AAFP); American Academy of Pain Medicine (AAPM); American Academy of Pediatrics (AAP); American College of Emergency Physicians (ACEP); American College of Physicians (ACP); American Dental Association (ADA); American Medical Association (AMA); American Osteopathic Academy of Addiction Medicine (AOAAM); American Psychiatric Association (APA); American Psychiatric Nurses Association (APNA); American Society of Addiction Medicine (ASAM); American Society for Pain Management Nursing (ASPMN); Association for Medical Education and Research in Substance Abuse (AMERSA); International Nurses Society on Addictions (IntNSA); National Association of Community Health Centers (NACHC); and the National Association of Drug Court Professionals (NADCP).

For more information: [www.pcssmat.org](http://www.pcssmat.org)

Twitter: [@PCSSProjects](https://twitter.com/PCSSProjects)

---

Funding for this initiative was made possible (in part) by Providers' Clinical Support System for Medication Assisted Treatment (1U79TI026556) from SAMHSA. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.