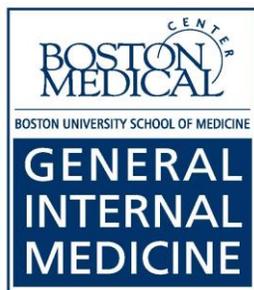
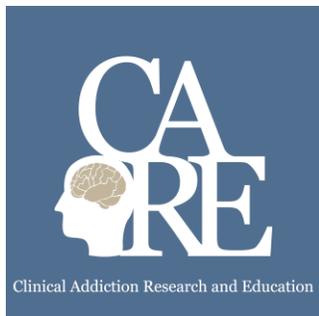


MAT TRAINING

PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

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

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Daniel Alford, MD, Disclosures

- 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.

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	Commercial Interest	What was received?	For what role?
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Accreditation Statement

- The American Society of Addiction Medicine (ASAM) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Designation Statement

- The American Society of Addiction Medicine (ASAM) designates this enduring material for a maximum of one (1) *AMA PRA Category 1 Credit*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.
 - Date of Release: December 22, 2015
 - Date of Expiration: July 31, 2018

System Requirements

- In order to complete this online module you will need Adobe Reader. To install for free click the link below:
 - <http://get.adobe.com/reader/>

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 of 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 opioid-dependent veterans 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

Trafton et al. 2000, Jamison et al. 2000, Rosenblum et al 2003

Karasz et al. 2004, Sharpe Potter J et al. 2010

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 addiction is not a barrier to successful opioid addiction 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

Martin J (1965), Ho and Dole V (1979), Compton P (1994, 2001), Meyer M (2007)

Pain and Addiction

Provider Perspective

1. Physicians Fear Deception

Physicians 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

Pain and Addiction

Patient Perspective

2. No Standard Approach

Patients perceive that the evaluation and treatment of pain and withdrawal is extremely variable among physicians. 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 physicians 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.”

Pain and Addiction

Patient Perspective

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

Peng PW, Tumber PS, Gourlay D: Can J Anaesthesia 2005
Alford DP, Compton P, Samet JH. Ann Intern Med 2006

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 addiction treatment

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., buprenorphine (Suboxone)) 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 addiction
- 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 as an Analgesic

- Parenteral and transdermal formulations approved for pain, **not** addiction treatment
 - **CANNOT** be used off-label under Drug Addiction Treatment Act of 2000
- Sublingual formulation approved for addiction, **not** pain treatment
 - Can be used off-label

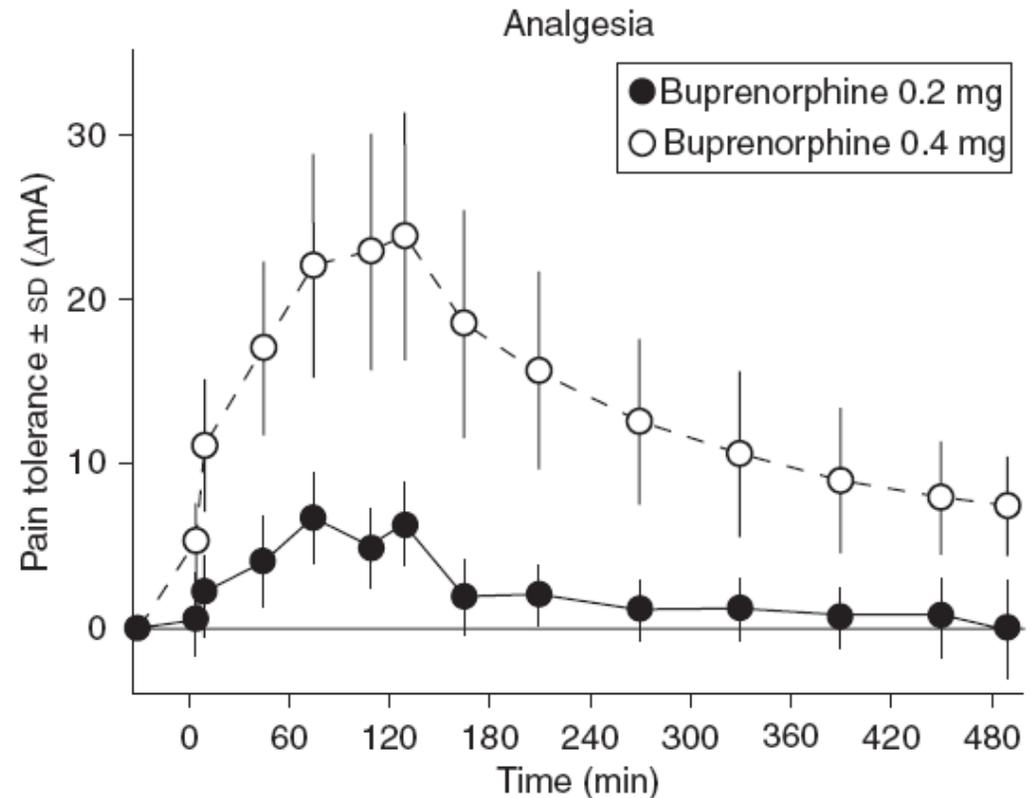
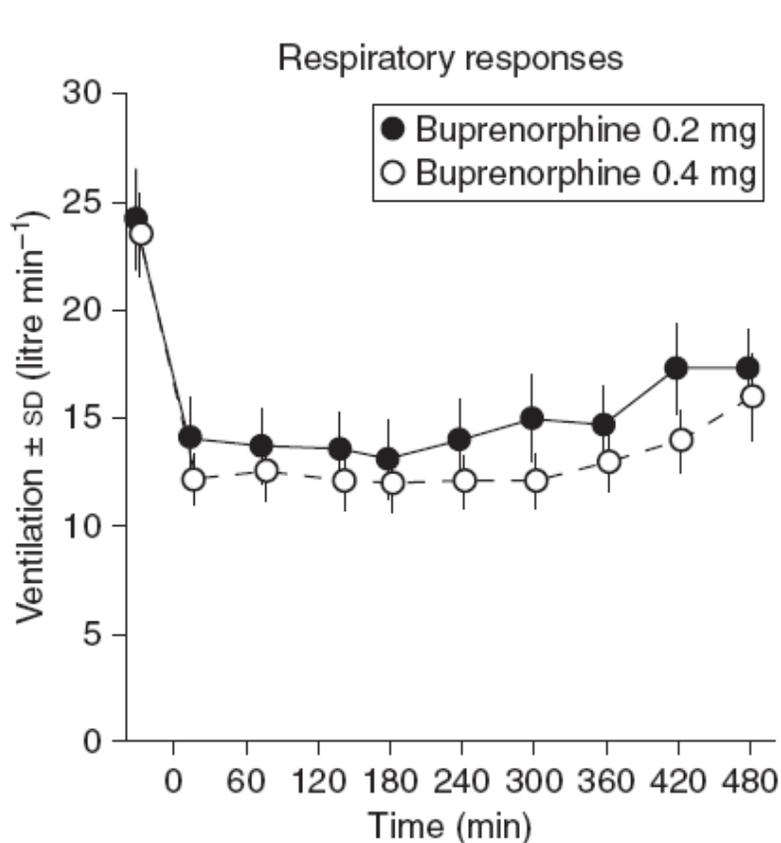
Buprenorphine as an Analgesic

- 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

Moa G et al. Acta Anaesthesiol Scand. 1990

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 or
 - 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

Kogel B, et al. European J of Pain. 2005

Englberger W et al. European J of Pharm. 2006

Acute Pain

Buprenorphine Maintenance Treatment *Options*

1. Continue buprenorphine and titrate short-acting opioid analgesic
2. D/c buprenorphine, use opioid analgesic, then re-induce
3. Divide total buprenorphine dose into every 6-8 hour dosing
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

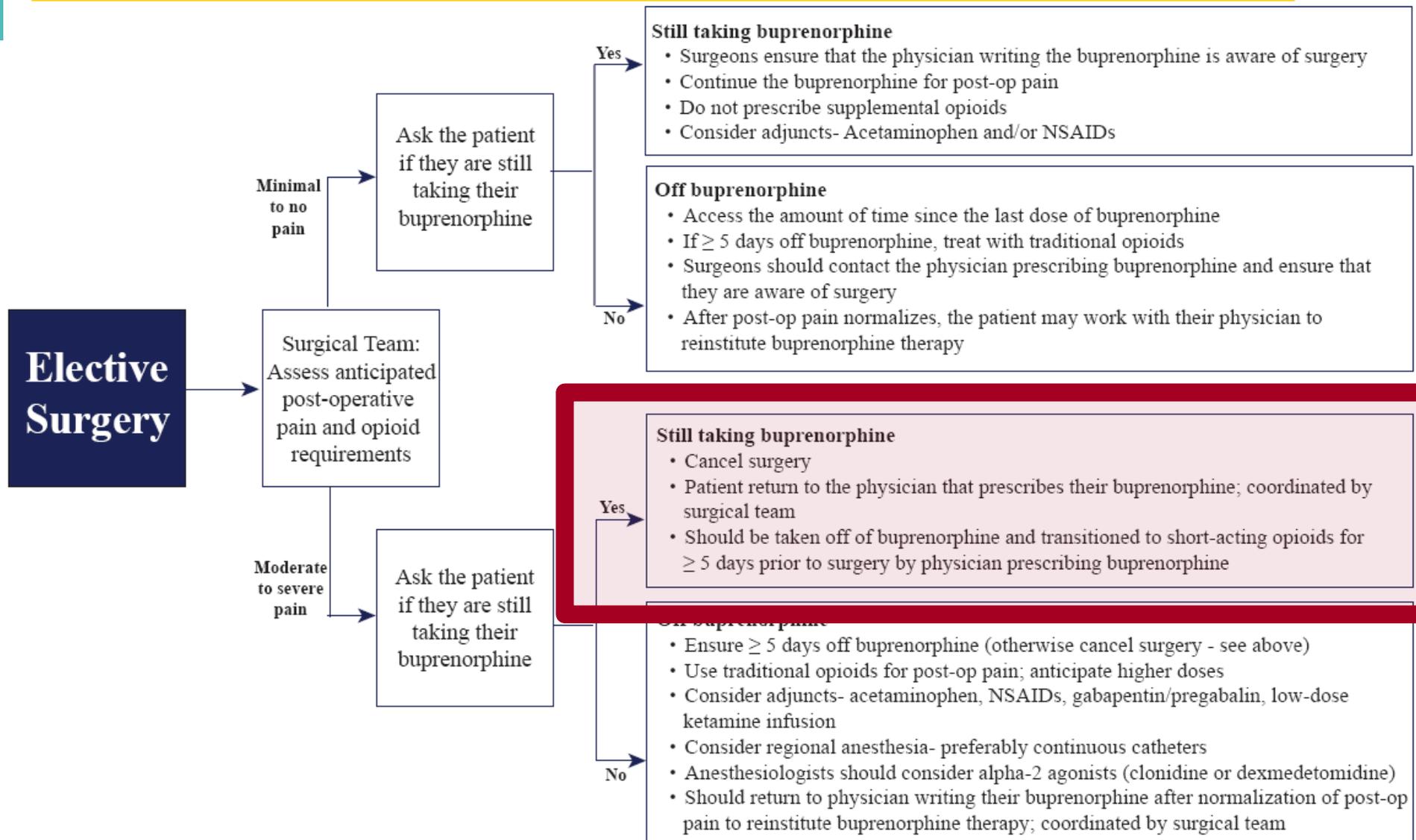
Alford DP. Handbook of Office-Based Buprenorphine Treatment of Opioid Dependence. 2010

Alford DP, Compton P, Samet JH. Ann Intern Med 2006

* Book SW, Myrick H, Malcolm R, Strain EC. Am J Psychiatry 2007

Buprenorphine Maintenance & Perioperative Pain Management

Management of Sublingual Buprenorphine (Suboxone and Subutex) in the Acute Perioperative Setting



The “Five Day” Rule

University of Michigan Protocol

- But this protocol...
 - Risks causing a disruption in the patient’s recovery from opioid addiction by stopping buprenorphine during high anxiety preoperative period
 - Has never been evaluated and is based on a theoretical concern of pharmacological principles

Boston Medical Center Management Guidelines



- 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

Boston Medical Center Management Guidelines

- **Post-procedure:** Opioid analgesics should be started using standard dosing protocols but pain management should be carefully monitored since patients with opioid use disorder often have decreased pain tolerance and cross-tolerance to opioid analgesics resulting in a need for higher opioid doses and shorter dosing intervals
- Because of its high affinity at the opioid receptor Fentanyl should be the opioid of choice for analgesia during surgery and in PACU for these patients

Boston Medical Center Management Guidelines

- Continue to hold buprenorphine
- All patients should be placed on an ER/LA opioid (e.g., SR morphine 15 mg bid) to address the patients baseline opioid requirements and for sustained pain control
- If patient also requires parenteral analgesia for breakthrough pain control use PCA (fentanyl, dilaudid or morphine) with NO basal dose. Continue ER/LA opioid
- If patient does not require parenteral analgesia for breakthrough pain control use IR/SA opioids e.g., oxycodone, morphine. Continue ER/LA opioid.

Boston Medical Center Management Guidelines

- Continue to hold buprenorphine
- All patients should be continued on ER/LA opioid
- Treat patient's breakthrough pain with IR/SA opioids e.g., oxycodone, morphine.
- Schedule patient to see their buprenorphine provider within 1 week to be considered for restarting buprenorphine maintenance

Does it need to be so
complicated?

Can it be as simple as managing
acute pain in methadone
maintained patients?

Acute Pain

Buprenorphine Maintenance Treatment Case Series

- 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)

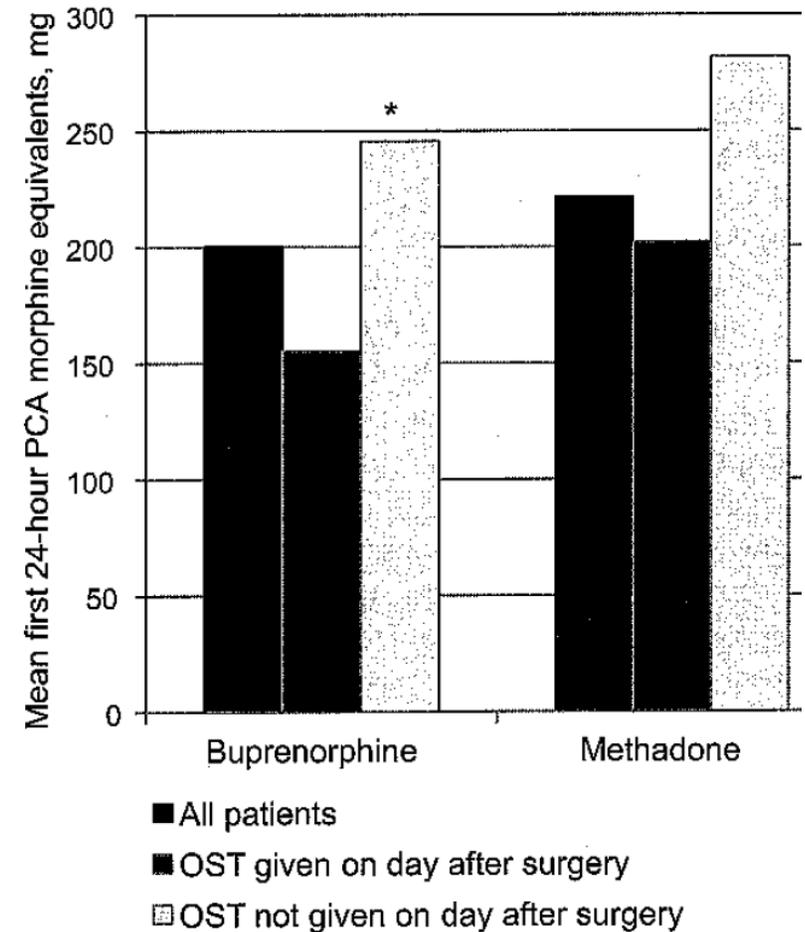
Hoflich AS et al. Eur J of Pain. 2011

Acute Pain

Buprenorphine Maintenance Treatment

Accumulating Research

- Retrospective cohort of 1st 24 hours after surgery in 11 BM and 22 MMT 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



Acute Pain

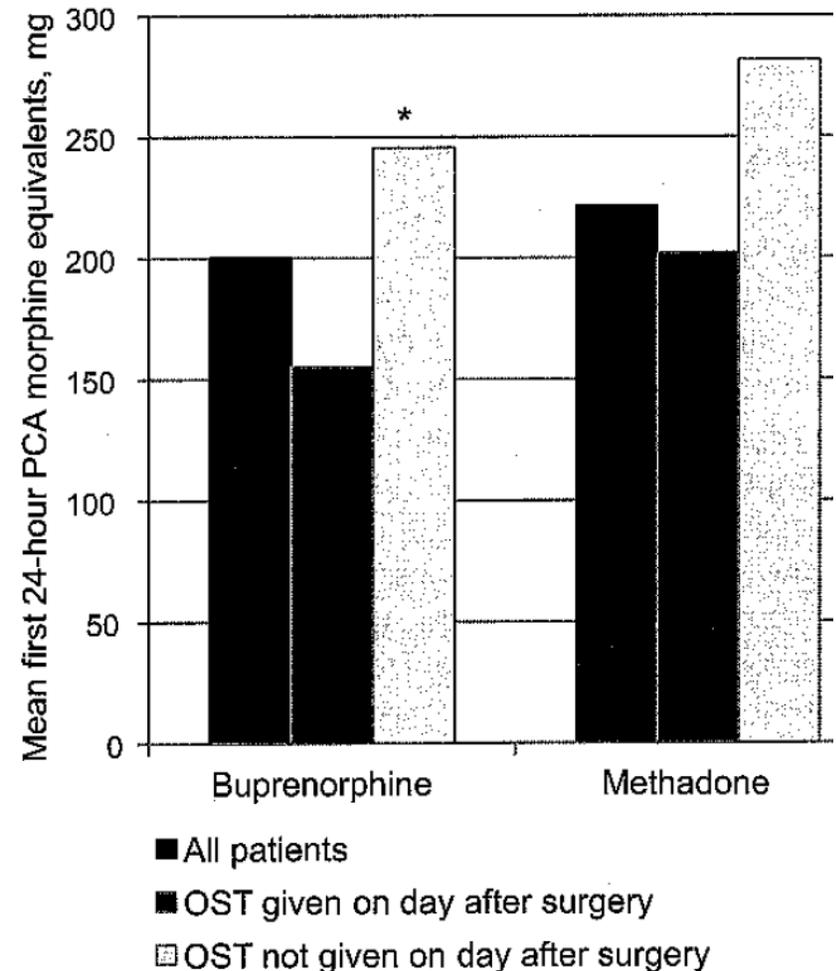
Buprenorphine Maintenance Treatment

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”



Buprenorphine Maintenance & Chronic Pain

Chronic Pain

Buprenorphine Maintenance Treatment

- 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

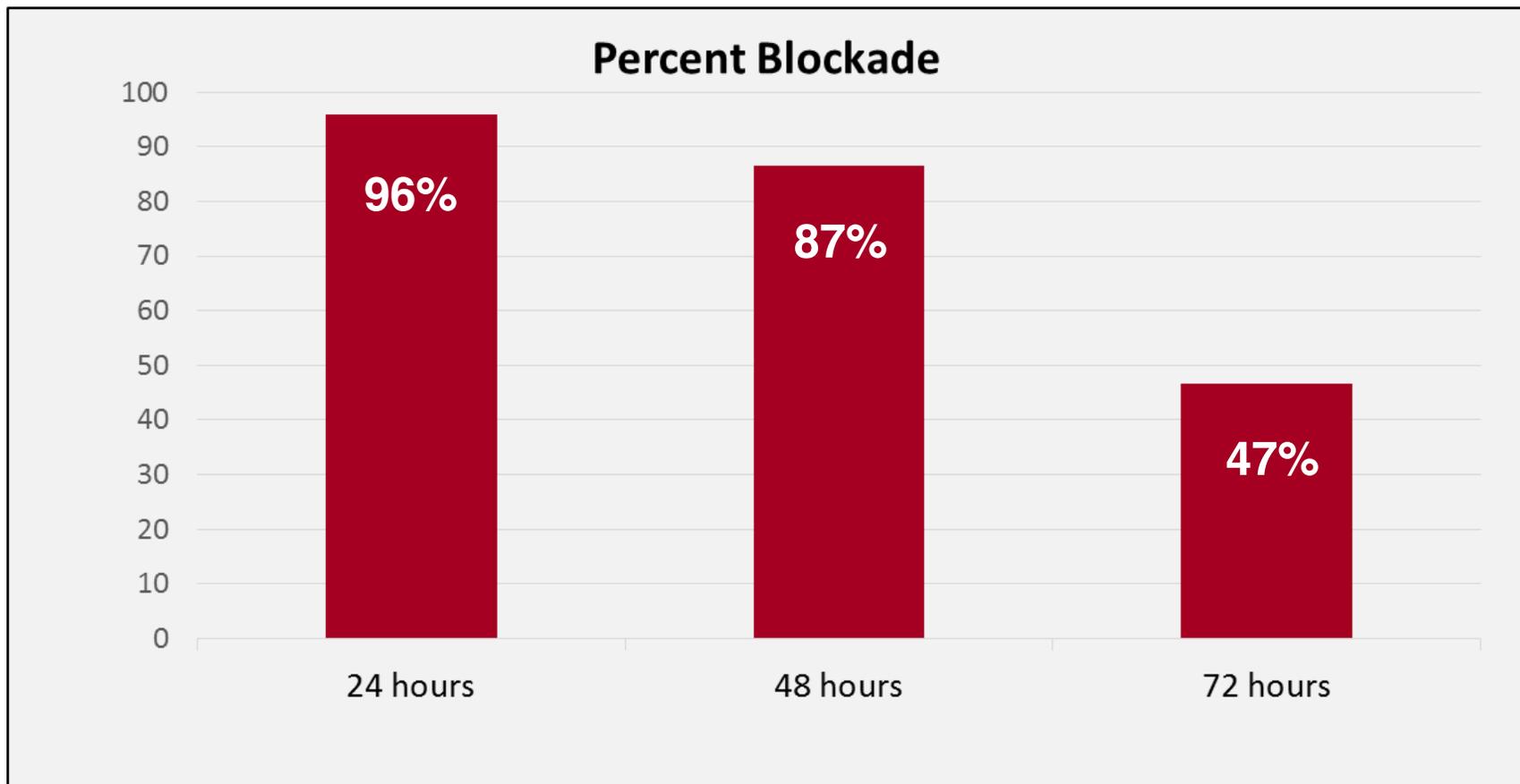
Buprenorphine Maintenance Treatment

- 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

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”



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

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 be prepared to establish and maintain a patient airway with assisted ventilation if needed
- Consider nonopioids and regional anesthesia

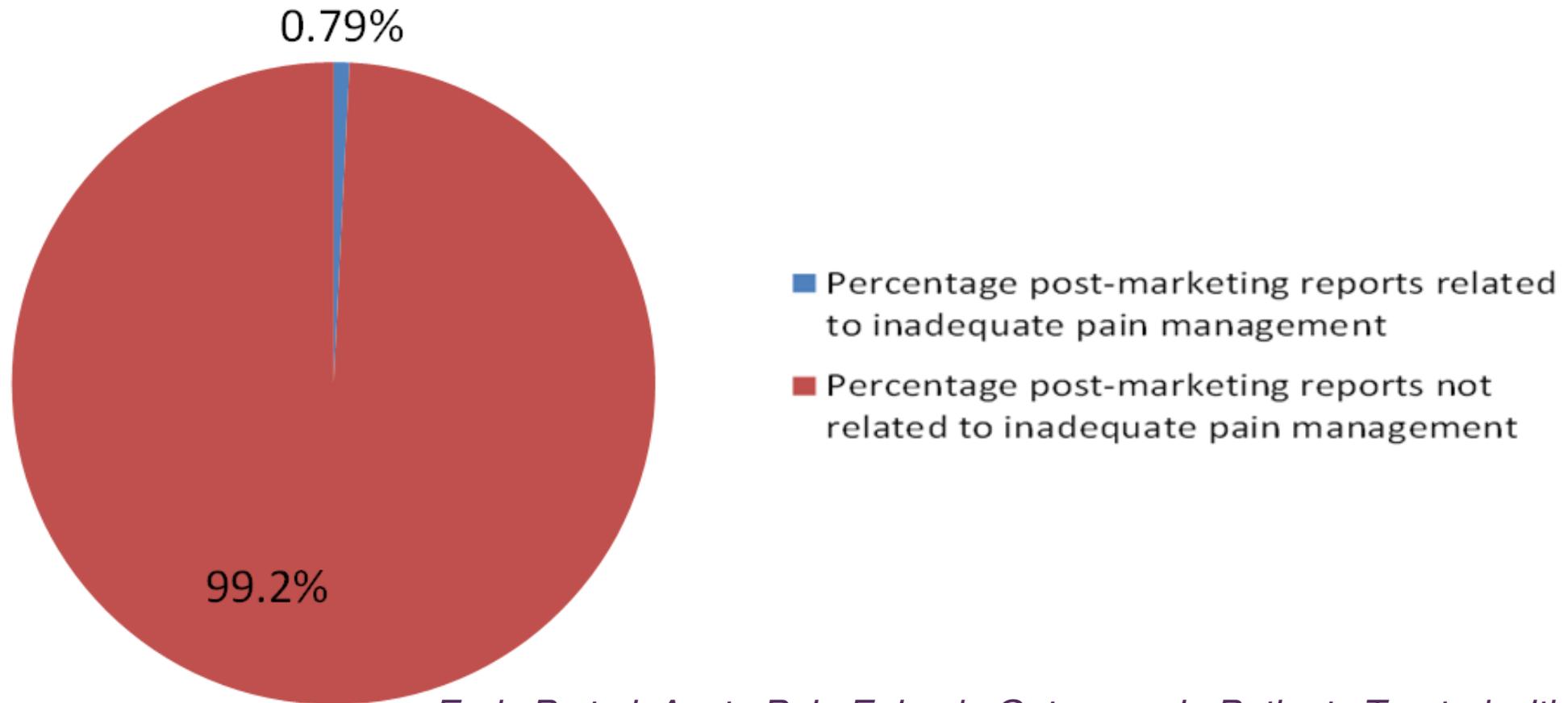
For more information on injectable naltrexone and pain management, call 1-888-235-8008 or visit

Vivitrolsafety.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 hours preoperatively
 - 50% of blockade effect is gone after 72hrs
 - **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

Percent of Pain-related Post-Marketing AE Reports



- Percentage post-marketing reports related to inadequate pain management
- 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-NTX) presented as poster at ASAM 2013 annual meeting

Study funded by Alkermes

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PCSS-MAT Mentoring Program

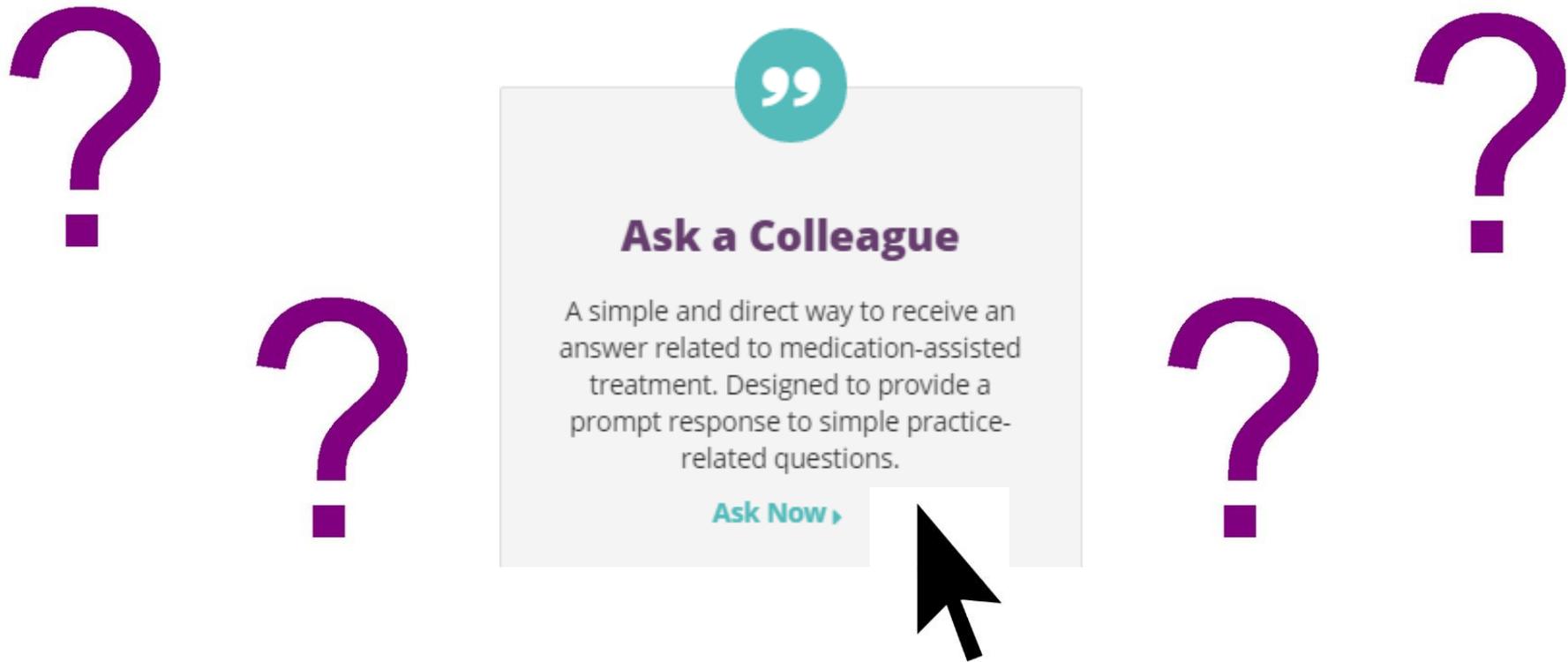
- PCSS-MAT Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid addiction.
- PCSS-MAT Mentors comprise a national network of trained providers with expertise in **medication-assisted treatment, addictions and 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 Listserv

Have a clinical question? Please click the box below!

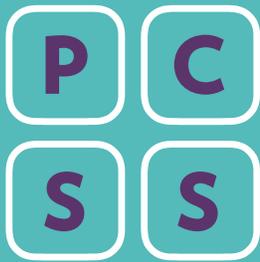


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MAT TRAINING

PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

PCSSMAT is a collaborative effort led by American Academy of Addiction Psychiatry (AAAP) in partnership with: American Osteopathic Academy of Addiction Medicine (AOAAM), American Psychiatric Association (APA), American Society of Addiction Medicine (ASAM) and Association for Medical Education and Research in Substance Abuse (AMERSA).

For More Information: www.pcssmat.org



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

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