MAT TRAINING
PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

Methadone: Its Role in Opioid Addiction Treatment vs. Pain Management

Yngvild Olsen, MD, MPH
American Society of Addiction Medicine
Kenneth B. Stoller, MD
American Association for the Treatment of Opioid Dependence
On behalf of

American Society of Addiction Medicine

Dr. Yngvild Olsen, Disclosures

Dr. Olsen 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.

Dr. Kenneth Stoller, Disclosures

Dr. Stoller 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.

ASAM Lead Contributors, CME Committee and Reviewers Disclosure List

Name	Nature of Relevant Financial Relationship		
	Commercial Interest	What was received?	For what role?
Yngvild Olsen, MD, MPH, FASAM	None		
Adam J. Gordon, MD, MPH, FACP, DFASAM, CMRO, Chair, Activity Reviewer	None		
Edwin A. Salsitz, MD, DFASAM, Acting Vice Chair	None		
James L. Ferguson, DO, DFASAM	First Lab	Salary	Medical Director
Dawn Howell, ASAM Staff	None		

ASAM Lead Contributors, CME Committee and Reviewers Disclosure List, Continued

Name	Nature of Relevant Financial Relationship		
	Commercial Interest	What was received?	For what role?
Noel Ilogu, MD, MRCP, FASAM	None		
Hebert L. Malinoff, MD, FACP, DFASAM, Activity Reviewer	Orexo Pharmaceuticals	Honorarium	Speaker
Mark P. Schwartz, MD, DFASAM, FAAFP	None		
John C. Tanner, DO, DFASAM	Reckitt-Benckiser	Honorarium	Speaker and consultant
Jeanette Tetrault, MD, FACP, FASAM	None		

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: July 15, 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 key pharmacological differences between methadone used for treatment of opioid addiction and its use in treating pain
  - Identify regulations unique to the use of methadone in treating opioid addiction compared to its use in treating pain
  - Understand the epidemiologic impact of methadone on morbidity and mortality related to opioid addiction compared to that related to pain

Outline

- History of methadone
- Pharmacology of methadone
  - Basic general and specific characteristics positive for pain and opioid addiction
  - Pharmacologic complexities
- Methadone dosing and monitoring considerations
- Methadone related regulations for pain and opioid use disorder treatment
- Epidemiology related to methadone for opioid use disorder and pain

Mr. A: A Case Vignette

- Mr. A, 27 year old Caucasian male, presented to an opioid treatment program (OTP) physician for admission after being started on methadone during a hospitalization for pain related to a severe left arm abscess requiring skin grafting.
- He has over a 10 year history of injection heroin use after initially starting with prescription opioids following a leg fracture at age 14.
- PMH: Opioid and tobacco use disorders, h/o multiple abscesses, hepatitis C
- Meds: methadone 20mg PO TID, gabapentin 300mg TID
- PE: well appearing male in NAD, alert, BP 112/60 HR 68 RR 12. Exam remarkable for track marks over right arm, left arm wrapped in clean, dry, and intact gauze, scattered well healed scars over right forearm and lower extremities.
  - How does the methadone dosing for pain differ from that in a typical OTP?
  - What information should the patient receive about his methadone?
  - How should practitioners outside of the OTP approach patients receiving methadone in an OTP?

History of Methadone

- Initially developed for analgesia in the 1930's as an analgesic alternative to morphine
- Acquired by US and introduced as analgesic and antitussive medication in 1947
- Innovated as treatment for opioid addiction beginning in 1964 by Drs. Vincent Dole and Marie Nyswander

Pharmacology of Methadone

General characteristics

- Lipid soluble with large volume of distribution leading to tissue build up
- Peak plasma concentration and effect occurs 2.5 to 4 hours after dose administration
- Elimination is mostly from hepatic metabolism by CYP450 3A4, 2D6, and 2B6
- Long elimination half life of 22-40 hrs with wide range (5-130 hrs)
- Renal and hepatobiliary excretion
  - Animal studies indicate hepatobiliary excretion becomes exclusive route in ESRD
  - Doses may need to be reduced in patients with ESRD and cirrhosis but clinical response should guide this

Key Pharmacological Properties of Methadone Compared to Morphine

	PO Bioavailability	Half-Life
Methadone	~80% (79 ±11.7%)	~30 hrs (30.4 ± 16.3)
Morphine	~30% (26 ±13%)	~3 hrs (2.7 ± 1.2)

Pharmacology of Methadone

- Positive characteristics for treatment of pain
  - High bioavailability
    - Active within 30 minutes of administration
  - No neurotoxic metabolites
    - EDDP is the major metabolite and is inactive
  - Activity at multiple receptor systems
    - Full mu-opioid agonist
    - NMDA antagonist
    - Serotonin reuptake inhibitor
    - Norepinephrine reuptake inhibitor

Pharmacology of Methadone

- Positive characteristics for treatment of opioid addiction
  - Long-acting for suppression of opioid withdrawal and craving
    - Allows for once daily dosing
  - Significant protein binding primarily by glycoproteins
    - Allows for constant serum levels over 24 hrs
    - Contributes to low level of methadone (<1% of daily dose) being removed by dialysis (PD or HD)
  - Orally effective
  - Activity at mu-opioid receptor
    - Slow offset and cross-tolerance allows for blockade effect and avoids rapid opioid withdrawal

Complexities of Methadone Pharmacology

- Variable hepatic metabolism
  - Multiple medication interactions – CYP450 system
  - Genetic variability
- Analgesic benefit shorter than respiratory depression and opioid withdrawal suppression effect
  - Accounts for limited analgesic effect with once daily dosing for opioid addiction
  - Contributes to respiratory depression risk, particularly in patients with obstructive sleep apnea
- No standard dose titration or equianalgesic conversion tables to/from other opioids
- Electrocardiogram changes: QTc prolongation with associated potential for Torsade de Pointe arrhythmia
- Due to tolerance to analgesic effects, patients on methadone maintenance may require HIGHER doses of opioid analgesia for acute pain management

Available Methadone Formulations

- All methadone formulations have the same pharmacologic properties
  - Liquid primarily used in opioid treatment programs
  - Scored 5mg and 10mg tablets are prescribed for pain and can be dispensed in OTPs for opioid use disorder (OUD)
  - Scored 40mg diskettes can only be dispensed in OTPs for OUD

Clinical Pearl

- Many of the pharmacological properties of methadone make it ideal for the treatment of opioid use disorder and a useful option for pain management but….
- Some of those same pharmacological properties also call for careful and close monitoring of dose adjustments, particularly during initial titration of the medication…..
- Especially since it takes five half-lives to reach steady state.

Methadone Dosing

Methadone dosing for **pain:**

- Use in patients with severe pain who need around-the-clock analgesia not otherwise controlled with non-opioid therapies
- "Start low and go slow"
  - If converting from another opioid, consider reducing morphine equivalent methadone dose by 75-90%
  - Recommended starting dose for opioid-naïve patients is 2.5mg q8 hrs
  - Titrate dose by no more than 5 mg every 5-7 days
- Advise patients not to double-up or unilaterally take extra doses if they miss a dose or experience inadequate analgesia
- Not typically first line medication for acute pain

Methadone Dosing

Methadone dosing for **opioid addiction:**

- For patients meeting diagnostic criteria for moderate to severe opioid use disorder
- Initial dose of 30-40mg once daily and slowly titrate (assuming some level of tolerance is present)
- Effective therapeutic dose range to suppress opioid withdrawal syndrome, reduce cravings, and block illicit opioid use is at least 60mg once daily, often closer to 80-85mg, but highly variable
  - Experimental and observational studies demonstrate higher frequency of opiate negative urine tests and less self-reported heroin use with doses of 80-100mg daily compared to 40-60mg
  - Clinical experience indicates that some patients may need doses above 100mg daily for optimal effect

Methadone Monitoring

Monitor for sedation during titration and regularly thereafter

- Sedation can precede respiratory depression so should be taken seriously
- Recommendation is to reduce dose

All patients should have toxicology testing done specifically for methadone

- Methadone does not cause an opiate positive toxicology test
- Urine is the most common but saliva testing is also available

Serum testing for methadone

- Too invasive for use as a screen

Can be useful in patients with OUD complaining of end of dose withdrawal symptoms but who have somnolence at peak effect

  - Obtain trough serum level 30 minutes prior to daily dose
  - Obtain peak serum level 2-3 hours after daily dose
  - If peak serum level is more than twice the trough level, patient may be a fast metabolizer and require split dosing for optimal effect

Regulations Governing Use of Methadone for Pain

- Schedule II controlled medication requiring active Provider DEA number
- Specific state policies
  - Prior insurance authorization may be needed
  - Specific CME requirements may be needed (e.g. Washington State)

- Practitioners can only *prescribe* methadone to treat pain (Controlled Substances Act, 1970)
  - All medication documentation needs to reflect its use for pain management

Regulations Governing Use of Methadone for Opioid Addiction

- Can only be *dispensed* to patients in an accredited specialized comprehensive Opioid Treatment Program (OTP)
- Layers of regulation
  - Federal regulations
    - DEA
    - SAMHSA
    - Accreditation bodies (e.g. TJC, CARF, COA)
  - State and/or local regulations often exist as well
- Patient criteria
  - Moderate to severe opioid use disorder
  - 18 years old or older
  - Able to provide informed consent
  - Current diagnosis of opioid use disorder, duration ≥ 1 year, unless pregnant or recently released/discharged from institutional setting and risk of relapse to opioid use is high

Epidemiologic Impact of Methadone for Pain

- Has documented efficacy in cancer pain comparable to morphine and fentanyl
- Is lower in cost than many other prescription opioids
  - 120 tablets of 10mg methadone ranges between $20-$40 on GoodRx
  - 120 tablets of 15mg MS Contin ranges between $60-$110 on GoodRx

- However…….

FDA Warnings - *Prescription* Methadone Overdose Deaths

- Overdose deaths from prescription opioids quadrupled from 4,030 deaths in 1999 to 16,651 in 2010.
- Almost one-third of prescription opioid overdose deaths involve methadone.
- Methadone accounts for only 2 percent of analgesic prescriptions in the United States.
- Methadone prescribed for pain contributes disproportionately to the excessive number of prescription opioid overdoses and associated medical and societal costs.

FDA Health Advisory

- Public Health Advisory 11/2006: Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat.
- Patients should take methadone exactly as prescribed.
- Patients taking methadone should not start or stop taking other medicines or dietary supplements without talking to their health care provider.
- Health care professionals and patients should be aware of the signs of methadone overdose.

Methadone Black Box Warning

- **Deaths, cardiac and respiratory,** have been reported during initiation and conversion of pain patients to methadone treatment from treatment with other opioid agonists. **It is critical to understand the pharmacokinetics of methadone** when converting patients from other opioids (see DOSAGE AND ADMINISTRATION). **Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration. Respiratory depression is the chief hazard** associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration. In addition, cases of **QT interval prolongation and serious arrhythmia (torsades de pointes)** have been observed during treatment with methadone. **Most cases involve patients being treated for pain with large, multiple daily doses of methadone,** although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Epidemiologic Impact of Methadone for Opioid Addiction

- Reduces risk of HIV by about six fold
- Reduces hepatitis C and B transmission
- Increases rates of employment
- Reduces criminal activity after 6 months or more of treatment
- Reduces illicit opioid use by 40% to 70%
- Increases length of life for patients with opioid addiction
- Reduces opioid overdose fatality rates by 40-80%

Methadone for Opioid Addiction and Chronic Pain Management

- Can be done in an Opioid Treatment Program (OTP)
  - May require exception request from CSAT and State Opioid Treatment Authority for split dosing
- Can be done outside of an OTP **only** if methadone is being prescribed primarily for chronic pain indication
- Methadone should not be only pharmacotherapy for chronic pain
  - Combine with non-opioid analgesic agents
  - Avoid benzodiazepines
- Additional behavioral interventions for chronic pain and opioid addiction should be provided
- Patient should receive education on treatment goals, methadone dosing, safety, and overdose prevention
  - Co-prescribe naloxone for opioid overdose reversal

Return to Mr. A: Case Vignette

Question from case vignette

How does the methadone dosing schedule differ from typical OTP dosing?

Clinical Pearl

Methadone dosing for treatment of opioid use disorder is typically once a day. Dosing for pain needs to be more frequent, often TID since the analgesic effect is shorter than the opioid withdrawal suppression effect.

Question from case vignette

What information should the patient receive about his methadone?

Clinical Pearl

Patients should be educated about key pharmacokinetic properties of methadone, including its tissue build up, analgesic effect compared to effect on respiratory depression and opioid withdrawal, timing of peak effect and its half life, concept of steady state, risk of medication interactions, common side effects and potential effect on QTc interval.

Return to Mr. A: Case Vignette

Question from case vignette

How should practitioners outside of the OTP approach patients being dispensed methadone in an OTP?

Clinical Pearl

Patients receiving methadone once daily in an OTP are taking this medication for the chronic disease of opioid addiction. This needs to be continued in other healthcare settings where the patient may receive care. If the patient is being treated for a pain condition, consider that the once daily methadone dose has reached steady state and is not likely to provide adequate analgesia.

If practitioners outside the OTP have concerns about side effects from the methadone or adverse effects due to combination with other medications or substances, or changes in the patient's health status, they should contact the physician at the OTP. They should also coordinate with the OTP whenever dose adjustments need to be made, and to coordinate logistically when discharging from inpatient hospital units.

References

- Center for Substance Abuse Treatment. (2005). Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Treatment Improvement Protocol (TIP) Series 43. HHS Publication No. (SMA) 12-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration.
- Chou R, Cruciani RA, Fiellin DA, Compton P, Farrar JT, Haigney MC, Inturrisi C, Knight JR, Otis-Green S, Marcus SM, Mehta D, Meyer MC, Portenoy R, Savage S, Strain E, Walsh S, Zeltzer L. (2014). Methadone Safety: A Clinical Practice Guideline From the American Pain Society and College on Problems of Drug Dependence, in Collaboration with the Heart Rhythm Society. J Pain, 15(4): 321-337.
- Clausen C, Waal H, Thoresen M, Gossop M. (2009). Mortality among opiate users: opioid maintenance therapy, age and causes of death. Addiction, 104:1356–1362.
- Controlled Substances Act. http://www.fda.gov/regulatoryinformation/legislation/ucm148726.htm
- Dole VP, Nyswander ME. (1966). Rehabilitation of heroin addicts after blockade with methadone. N Y State J Med, 66: 2011-7.
- Eap CB, Buclin T, Baumann P. (2002). Interindividual Variability of the Clinical Pharmacokinetics of Methadone. Clin Pharmacokinet, 41(14): 1153-1193.
- Food and Drug Administration. (2006). Public Health Advisory: Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat. http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm124346.htm
- Friedman RJ. (2011). Understanding the New Washington State Pain Medication and Opioid Rules. http://www.lanepowell.com/wp-content/uploads/2011/06/OpioidRuleComments1.pdf
- General Accountability Office: Methadone-associated overdose deaths: Factors contributing to increased deaths and efforts to prevent them. http://www.gao.gov/products/GAO-09-341

References

- Gibson A., Degenhardt L., Mattick R. P., Ali R., White J., O'Brien S. (2008). Exposure to opioid maintenance treatment reduces long-term mortality. Addiction, 103: 462–8.
- Good P, Afsharimani B, Movva R, Haywood A, Khan S, Hardy J. (2014). Therapeutic Challenges in Cancer Pain Management: A Systematic Review of Methadone. J Pain Palliat Care Pharmacother, 28(3): 197-205.
- Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. (2000). A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. N Engl J Med, 343(18):1290-7.
- Loimer N, Schmid R. (1992). The use of plasma levels to optimize methadone maintenance treatment. Drug Alcohol Depend, 30: 241-246.
- Metzger DS, Woody GE, McLellan AT, O'Brien CP, Druley P, Navaline H, DePhilippis D, Stolley P, Abrutyn E. (1993). Human immunodeficiency virus seroconversion among intravenous drug users in- and out-of-treatment: an 18-month prospective follow-up. J Acquir Immune Defic Syndr, 6(9):1049-56.
- Tsui JI, Evans JL, Lum PJ, Hahn JA, Page K. (2014). Association of opioid agonist therapy with lower incidence of hepatitis C virus infection in young adult injection drug users. JAMA Intern Med, 174(12):1974-81.
- Wong E, Walker KA. (2012). A review of common methods to convert morphine to methadone. J Community Hosp Int Med Perspect, 2(4):19541.
- Zahari A, Lee CS, Ibrahim MA, Musa N, Mohd Yasin MA, Lee YY, Tan SC, Mohamad N, Ismail R. (2016). Relationship between ABCB1 polymorphisms and serum methadone concentration in patients undergoing methadone maintenance therapy (MMT). Am J Drug Alcohol Abuse, Jun 10: 1-10.

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.

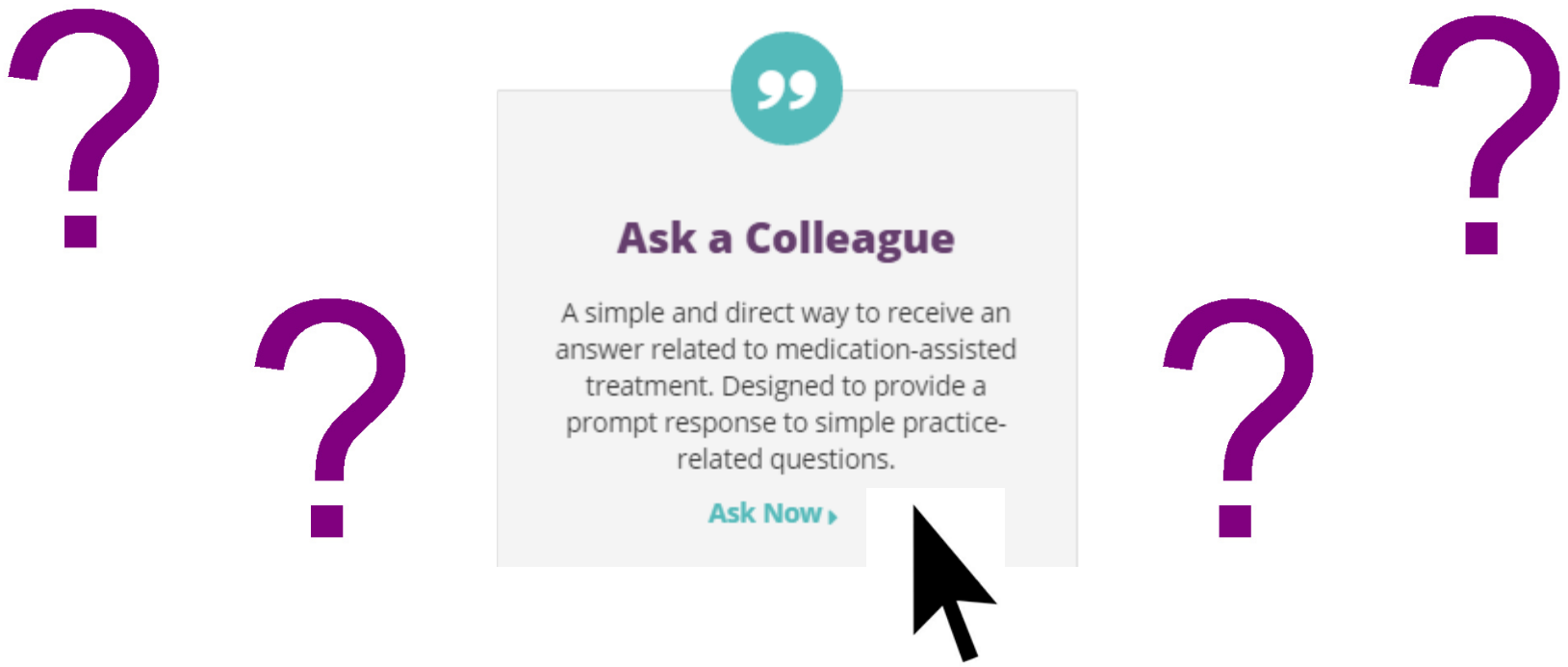
For more information on requesting or becoming a mentor visit:

pcssmat.org/mentoring

PCSS MAT TRAINING
PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

PCSS-MAT Listserv

Have a clinical question? Please click the box below!



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

Funding for this initiative was made possible (in part) by Providers' Clinical Support System for Medication Assisted Treatment (5U79TI024697) 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.

Please Click the Link Below to Access the Post Test for this Online Module

Click here to take the Module Post Test

Upon completion of the Post Test:

- If you pass the Post Test with a grade of 80% or higher, you will be instructed to click a link which will bring you to the Online Module Evaluation Survey. Upon completion of the Online Module Evaluation Survey, you will receive a CME Credit Certificate or Certificate of Completion via email.

- If you received a grade of 79% or lower on the Post Test, you will be instructed to review the Online Module once more and retake the Post Test. You will then be instructed to click a link which will bring you to the Online Module Evaluation Survey. Upon completion of the Online Module Evaluation Survey, you will receive a CME Credit Certificate or Certificate of Completion via email.

- After successfully passing, you will receive an email detailing correct answers, explanations and references for each question of the Post Test.