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HEALTH

(MOUD): Recommendations for Medication Selection and Management

Summary:

These recommendations are for treating adults with opioid use disorder (OUD) with the following mediations for opioid use disorder (MOUD): methadone, buprenorphine, and extended-release naltrexone. They include consideration of:

- The selection/choice of medication and formulation;
- The selection of induction site (at "home" or in office); and
- Monitoring, follow up, and safety concerns.

These recommendations are educational in nature and include general recommendations only; specific clinical decisions should only be made by a treating clinician based on the individual patient's clinical condition. Related resources for providers are included.

Contents

1. Diagnosing Opioid Use Disorder (OUD)

a. Screen for Opioid Use Disorder.

The Substance Abuse and Mental Health Services (SAMHSA) Treatment Improvement Protocols recommend universal screening for opioid use disorder. In June 2020, the US Preventative Services Task Force (USPSTF) published its recommendation to screen adults ages 18 or older by asking questions about unhealthy drug use. According to SAMHSA, a single question screener can be used to efficiently screen for opioid misuse. Any response other than zero is considered a positive screen:

> *How many times in the past year have you used an illegal drug or a prescription medication for nonmedical reasons?*

Validated screening instruments are available to follow up on positive screens. Advancing Drug and Opioid Prevention and Treatment (ADOPT), is a SAMHSA-funded training initiative that has publishes an overview of the various screening instruments available.

b. Use DSM-5 clinical diagnostic criteria for OUD.
c. Obtain a urine drug screen (UDS).
    i. If negative for opioids (including buprenorphine), OUD may be in remission (tenuous or stable) or a diagnosis of OUD may be inaccurate; seek collateral information on OUD diagnosis (to avoid someone without an OUD trying to get buprenorphine to sell or use for other reasons). Collateral information includes:
        1. Information from case managers or family on patient's opioid use
        2. Prior health care documentation (e.g., ER visits; OUD-related sequelae e.g., abscesses, infective endocarditis, overdoses)

2. Medication to treat MOUD (defined in summary section) Options: Advantages/Disadvantages and Treatment Selection Criteria

Class and Behavior:

Methadone	Buprenorphine	Naltrexone
Agonist: binds to opioid receptors in the brain and act like opioids within the body	Partial Agonist: binds to opioid receptors in the brain and act like opioids within the body	Antagonist: blocks opioid receptors to the brain

Advantages:

Methadone	Buprenorphine	Naltrexone
- If prescriptions are properly followed, highly effective in reducing cravings, withdrawals, and relapse to illicit opioid use. - Regulated, since dosing is administered. - No needle sharing reduces chances of contracting disease. - Less potential for criminal activity (e.g. selling, trading)	- May be prescribed by certified outpatient providers, which lowers the time patient must spend at clinics. - Effective in decreasing cravings and relapse. - Less intoxicating effect than illicit opioids.	- Has no sedating, or addictive effect. - No physical dependence. - With injectable form, a daily dose is not needed - Reduces relapse.

Disadvantages:

Methadone	Buprenorphine	Naltrexone
- Can be abused. - Often has side effects. - Physiologically addictive. - Requires daily visits to the clinic. - Long term treatment. - If doses are missed, increased risk of relapse. - Short and long term side effects including vomiting, itchy skin, and slow breathing.	- Can be abused. - Can be used illegally since it has "street" value. - Some sedating/ intoxicating effects. - Withdrawal occurs upon cessation. - Can be viewed as continuing opioid habits at moderate capacity.	- Requires 7-day abstinence period prior to administration – many people have difficulty meeting this requirement. - Injectable and implant forms are expensive. - Reduced compliance with oral Naltrexone.

Real World Insights:

- One of the barriers to methadone maintenance treatment is the perception of its impact on the lives of those in treatment, with terms such as 'liquid handcuffs' or "methadone shuffle" used to describe it. Individuals receiving methadone can only be treated by a federally-licensed opioid treatment program (OTP) and must be seen daily for observed medication administration. OTPs have long been siloed from the traditional healthcare system – both geographically and organizationally – which only adds to the stigma associated with methadone treatment. Integrating methadone treatment into mainstream healthcare with primary care and pharmacist prescribing, which occurs in Canada and Europe, could help address this barrier and improve access to and uptake of treatment.

- One psychological effect of methadone treatment reported in clinical practice is that individuals who have been treated with methadone have a flat, depressed, detached affect and seem 'disconnected from the world.' These effects are reported as particular to methadone and not seen with

Candidates:

Methadone	Buprenorphine	Naltrexone
- Patients who need daily support - Patients having multiple unsuccessful prior treatments - Moderate to severe OUD patients	- First line of treatment for most patients - Moderate to severe OUD patients	- Patients who cannot use agonists - Mild OUD patients

Contraindications:

Methadone	Buprenorphine	Naltrexone
- Hypersensitivity or allergy - Respiratory depression - Severe bronchial asthma or hypercapnia - Patients with abnormally high carbon dioxide blood levels - Paralytic ileus - Cardiopulmonary disease - High risk polypharmacy: benzodiazepines, sedatives - Alcohol dependence	- Hypersensitivity or allergy - Active alcohol dependence - Abuse of sedative hypnotics - Hepatitis C or high liver function testing - HIV anti-retroviral medication - Cirrhosis - Major Depressive Disorder	- Patients currently physically dependent on opioids, including partial agonists - Patients receiving opioid analgesics - Patients in acute opioid withdrawal - Hypersensitivity - Renal impairment - Hepatitis C or high liver function testing

Real World Insights:

- Buprenorphine: Individuals who are homeless may need prescribing in smaller increments (e.g. one week at a time) as they can experience difficulties related to medication adherence, diversion, and abuse.
- Naltrexone: In practice, suicidal ideation and suicidal thoughts can increase with naltrexone use and patients should be monitored for the emergence of depressive symptoms. Individuals who have attempted suicide or have serious depression may be non-candidates for treatment.
- Guidance on clinically relevant drug interactions for buprenorphine or methadone is available from the Providers' Clinical Support System for Medication Assisted Treatment.

3. Dosing, Induction, and Administration

Dosing

Methadone	Buprenorphine	Naltrexone
- 60 – 100 mg per day	- FDA Approved: 8 – 32 mg per day - Recommended: 8 – 16mg per day	- Oral dose: 50 – 100 mg per day - Injectable dose: 380 mg IM every 4 weeks

Dosage Forms

Methadone	Buprenorphine	Naltrexone
- Liquid - Dispersible tablets - Tablets	- Sublingual film, or tablet - Buccal film - Long-acting injection, - or implant	- Long-acting injection

Induction and Administration

Methadone	Buprenorphine	Naltrexone
- Patient can start at anytime	- Patient has mild to moderate withdrawal symptoms (Clinical Opiate Withdrawal Scale (COWS) score 6-10)	- Patient must have not used opioids for 7 days for short-acting opiates and 10-14 days for long-acting opiates prior to starting
- Administered daily at federally licensed opioid treatment programs (OTPs)	- Since it has low overdose risk, does not require daily dosing administration - At home or at office	- Monthly injection - At office

Real World Insights:

- **Methadone**
    - Must be administered in a federally-licensed OTP
    - Individualized dose adjustment and daily monitoring of response to treatment is advised to avoid methadone intoxication and overdose death.

- **Buprenorphine**
    - Options for buprenorphine induction:
        - Unobserved in-home induction
        - Patient selection criteria: patients with a good support system who may also wish a more private setting and/or have concerns regarding transportation; this option is best for those who can follow instructions and will not take medication too early.
        - In-office induction ("medically-supervised withdrawal")
        - Patient selection criteria: poor support system
    - Extended-release formulations
        - Monthly extended-release buprenorphine injection formulation is FDA-approved for patients with moderate-to-severe OUD who have been initiated and treated with transmucosal buprenorphine for at least 7 days.
        - Medication is for subcutaneous abdominal injection by a healthcare provider only.
    - Detailed guidance on buprenorphine induction and dosing is provided by the Provider Clinical Support System for Medication Assisted Treatment Guidance for Buprenorphine Induction.

- **Naltrexone**
    - Only extended-release naltrexone is FDA-approved to treat OUD.
    - Extended-release naltrexone is administered by provider injection, so inductions are officed-based.
    - Detailed guidance on treatment of OUD with extended-release naltrexone is provided by the Provider Clinical Support System for Medication Assisted Treatment XR-Naltrexone: A Step-by-Step Guide.

4. Monitoring and Follow-up

Methadone	Buprenorphine	Naltrexone
- Treatment should include relapse monitoring with frequent testing for substance use. - Testing for methadone and buprenorphine is recommended to detect possible diversion.	- Urine drug testing - Weekly visits to the office until stable - PDMP data must be reviewed - To reduce diversion, frequent visits, observed dosing, recall visits for pill counts, and urine drug tests are advised.	- Urine drug testing - PDMP data is recommended to be reviewed - Conduct active outreach to schedule monthly visits for monitoring and injections.

- **Urine Drug Screening assays**
    - 2 types are used, depending on the stage of care and clinical management objective:
        - Point-of-Care testing aka "Qualitative UDS (Presumptive drug testing)"
            - Typically done on-site, with rapid results
            - Billing codes 80305, 80306, 80307
        - Confirmatory Drug testing
            - Typically done off-site, at a reference lab
            - The values are typically quantitative and include multiple drug classes as well as some metabolites (such as norbuprenorphine).
            - Billing codes G0481, G0482, G0483
    - Caveats (from SAMHSA TIP 63, Medications for Opioid Use Disorder, 2018)
        - Opiate screen
            - Codeine and morphine will screen positive
            - Tramadol can cause a false positive
            - buprenorphine and methadone will screen negative
            - Fentanyl and oxycodone will screen negative
            - Hydromorphone and hydrocodone will often screen negative
        - Amphetamine screen
            - False positives with bupropion, chlorpromazine, desipramine, fluoxetine, labetalol, promethazine, ranitidine, pseudoephedrine, trazadone and other common medications. Check unexpected positives with the lab.

- Benzodiazepine screen
    - False positives with sertraline and oxaprozin
    - Frequent false negatives with therapeutic dosing of clonazepam and lorazepam, due to low sensitivity.

5. Management of Withdrawal Symptoms

Symptom	Medication
Nausea	Ondansetron, metoclopramide (avoid promethazine; it potentiates opioids)
Diarrhea	Loperamide
Anxiety, irritability, sweating	Clonidine
Insomnia	Diphenhydramine, trazodone
Pain	Nonsteroidal anti-inflammatory drugs

6. Safety Concerns and Possible Adverse Effects

Methadone	Buprenorphine	Naltrexone
- Associated with increased risk of adverse effects, including prolongation of the QT interval and other arrhythmias, which in - some cases have been fatal. - High risk polypharmacy: benzodiazepines, sedatives - Pregnancy	- Patients who discontinue antagonist therapy and resume opioid use increase risk associated with an opioid overdose and death. - Side effects: headache, anxiety, constipation, perspiration, fluid retention in lower extremities, urinary hesitancy, and sleep disturbance	- Patients who discontinue antagonist therapy and resume opioid use increase risks associated with an opioid overdose and death. - Side effects: insomnia, lack of energy/sedation, anxiety, nausea, vomiting, abdominal pain/cramps, headache, cold symptoms, joint and muscle pain, and specific to extended-release injectable naltrexone injection site reactions - Suicidal thoughts, depression

7. Duration of Treatment / Treatment Discontinuation

- There is no established duration for methadone treatment - Recommended to continue at least 12 months.	After patient has achieved … - Employment, engagement in mutual help programs, or involvement in other meaningful activities. - Sustained abstinence from opioid and other drugs during treatment. - Positive changes in the psychosocial environment. - Evidence of additional psychosocial supports. - Persistent engagement in treatment for ongoing monitoring past the point of medication discontinuation. - Recommended to continue at least 12 months. - When patient is stable and chooses to taper, recommend reducing gradually, the daily dose by 2 mg, every 2-4 weeks, as tolerated.	- Recommended to continue at least 3 to 4 months.

8. Panel Review Process

On a monthly basis, consider generating a MOUD panel report that identifies:

- Patients needing call-backs (if not seen recently)

- Patients needing PCP switches (ideally the longitudinal prescriber will also be the PCP, if feasible)
- Buprenorphine patients need norbuprenorphine screening (twice in 1st month of prescribing, then at least every 6 months afterwards)
- Ensuring that the number of active patients on a provider's panel of Buprenorphine patients does not exceed that provider's limit (30 vs 100) – cross off patients not active on their panel (e.g., transferred care, lost to follow-up, cross-coverage prescription only) and then count the remainder

9. Common Challenges

- Ongoing use of illicit opioids, but with adherence to office visits
    - Consider a MOUD dose increase
    - Screen for diversion - a patient may be taking a lower dose (and thus with more opioid cravings) and diverting the rest
    - Try to quantify benefits and reduced harms
        - Using less illicit opioids? (per patient report AND urine drug screens)
        - Less ER visits?
        - Improved engagement in other aspects of care?
        - Improved work or family situation?
    - Consider extended-release naltrexone, or referral to methadone therapy
    - It is acceptable to continue OUD treatment if there are objective benefits to treatment
- Persistent use of non-opioids, such as stimulants (methamphetamine, crack/cocaine), benzodiazepines, or alcohol, in setting of adherence to visits and improvements in illicit opioid use
    - It is recommended that buprenorphine NOT be discontinued solely due to the presence of a concurrent, untreated non-opioid substance use disorder, including benzos
    - Buprenorphine is not a treatment for other non-opioid use disorders, and is not expected to improve outcomes for these other use disorders
    - If alcohol use is ongoing:
        - Consider transitioning to extended-release naltrexone
        - Consider use of medication-assisted treatment for alcohol use disorder: gabapentin, acamprosate, topiramate
        - Continue visits weekly or more often
    - If benzodiazepine use is ongoing:
        - Consider weekly or more often visits
        - Pharmacotherapy with non-benzos for anxiety disorders or PTSD
    - Referral for psychosocial interventions for the concurrent substance use disorders
- Requests for higher doses
    - If illicit opioid use is suppressed, avoid dose increases of buprenorphine.

10. Relapse: Addressing Relapse to Illicit Opioid Use

Relapse to illicit opioid use and treatment discontinuation are common. Strategies to address relapse include:

- Behavioral therapy
- Consider changing type of treatment or formulation (e.g. change from oral to long-acting injectable)
- Increase dosage

Real World Insights:

- When individuals who are engaged in outpatient treatment for OUD engage in illicit opioid use, inpatient or 'residential' treatment may be helpful.
    - However, individuals receiving methadone treatment who engage in illicit opioid use have difficulty getting into inpatient treatment for the following reasons:
        - Many residential programs require patients to transition to buprenorphine, so patients must taper their methadone dose, which precipitates withdrawal symptoms.
        - Medicaid does not pay for residential treatment.
    - In many instances, individuals who relapse experience increased outpatient dosing, increased monitoring, and/or revocation of probation and possible jail time, but these interventions do not lead to successful discontinuation of illicit opioid use.
    - There is a need for strategies to support people in their recovery that go beyond the usual responses

11. Procurement and Use in Hospital and Healthcare Settings

- Healthcare providers can procure MOUD through wholesalers and group purchasing organizations (GPOs) who contract with manufacturers, or directly from manufacturers.
- Methadone
    - Under the Certification of Opioid Treatment Programs, 42 Code of Federal Regulations (CFR) 8, patients may be treated with scheduled narcotics for maintenance treatment of OUD only by an Opioid Treatment Program (OTP), which is governed by state and federal licenses.
    - Hospitals can administer methadone in the inpatient setting to treat or prevent opioid withdrawal or OUD.
- Buprenorphine
    - Oral formulations are available through regular pharmacy channels.
    - Sublocade, the long-acting injectable formulation, is available through specialty pharmacy channels.

Real World Insights:

- Provider Access
    - Providers order and prescribe medications through electronic health record (EHR) systems.
    - The availability of MOUD, like other medications, is governed by the hospital or health system Pharmacy and Therapeutics (P&T) Committee, a subcommittee of the Medical Executive Committee.
    - The P&T Committee makes decisions about which drugs to include on the hospital or health system formulary.
    - The pharmacy department is responsible for procurement and building order sets in the EHR, in conjunction with the Information Services (IS) department.

Resources

Providers Clinical Support System

https://pcssnow.org/

PCSS is a program funded by the Substance Abuse and Mental Health Services Administration (SAMHSA) created in response to the opioid overdose epidemic to train primary care providers in the evidence-based prevention and treatment of opioid use disorders (OUD) and treatment of chronic pain. The project is geared toward primary care providers who wish to treat OUD.

Advancing Drug and Opioid Prevention and Treatment, Online Resources and Trainings

https://opioidpreventionandtreatment.ucsf.edu/

Project Advancing Drug and Opioid Prevention and Treatment (ADOPT) is a collaborative, multidisciplinary training initiative that includes physicians, nurse practitioners, and psychologists at 3 distinct universities and over 300 Northern California training clinics. The purpose of this project is to improve opioid use disorder (OUD) outcomes in California by increasing the workforce of waivered, culturally competent medication-assisted treatment (MAT) providers and supporting the development of MAT-prepared clinics to remote and underserved regions.

Screening Tool Pamphlet:

https://opioidpreventionandtreatment.ucsf.edu/sites/g/files/tkssra506/f/wysiwyg/ScreenersPamphlet_10_21_19%20.pdf

Decisions in Recovery: Treatment for Opioid Use Disorder:

https://mat-decisions-in-recovery.samhsa.gov/section/which.aspx

An online tool has been developed to inform patients about MAT, compare treatment options, decide which option is best for the patient, and discuss options and preferences with a healthcare provider. The tool provides numerous resources to guide patients through the road to recovery: https://mat-decisions-in-recovery.samhsa.gov/ This decision support tool was developed with funding from the federal Substance Abuse and Mental Health Services Administration (SAMHSA). It was prepared by the Center for Social Innovation with Advocates for Human Potential, Inc. under Bringing Recovery Supports to Scale Technical Assistance Center Strategy (BRSS TACS); contract number HHSS 280201100002C, SAMHSA, U.S. Department of Health and Human Services (HHS).

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Real World Insights were obtained through interviews with healthcare personnel with relevant experience.