Guideline Title	
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GUIDELINE OVERVIEW - This TIP (Treatment Improvement Protocol 63) reviews three Food and Drug Administration-approved medications for opioid use disorder treatment—methadone, naltrexone, and buprenorphine—and the other strategies and services needed to support people in recovery. Each FDA-approved medication used to treat OUD can help patients achieve remission and begin or maintain recovery. Medication for OUD should be accompanied by *individually tailored medical management and psychosocial and recovery support services* as needed and wanted by patients to support their remission and recovery. Medication supports the efforts of the individual to achieve lasting recovery. This TIP cannot replace sound clinical judgment and shared decision making based on careful patient assessment.

Part 1: Introduction to Medications for Opioid Use Disorder Treatment:

• Increasing opioid overdose deaths, illicit opioid use, and prescription opioid misuse constitute a public health crisis.
• OUD medications reduce illicit opioid use, retain people in treatment, and reduce risk of opioid overdose death better than treatment with placebo or no medication.
• Only physicians; nurse practitioners; physician assistants; and, until October 1, 2023, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives can prescribe buprenorphine for OUD. They must get a federal waiver to do so.
• Only federally certified, accredited OTPs can dispense methadone to treat OUD. OTPs can administer and dispense buprenorphine without a federal waiver.
• Any prescriber can offer naltrexone.
• OUD medication can be taken on a short- or long-term basis, including as part of medically supervised withdrawal and as maintenance treatment.
• Patients taking medication for OUD are considered to be in recovery.
• Several barriers contribute to the underuse of medication for OUD.

Part 2: Addressing Opioid Use Disorder in General Medical Settings:

• All healthcare practices should screen for alcohol, tobacco, and other substance misuse (including opioid misuse).
• Validated screening tools, symptom surveys, and other resources are readily available.
• When patients screen positive for risk of harm from substance use, practitioners should assess them using tools that determine whether substance use meets diagnostic criteria for a substance use disorder (SUD).
• Thorough assessment should address patients' medical, social, SUD, and family histories.
• Laboratory tests can inform treatment planning.
• Practitioners should develop treatment plans or referral strategies (if onsite SUD treatment is unavailable) for patients who need SUD treatment.

Part 3: Medications for Opioid Use Disorder:

• OUD medications are safe and effective when used appropriately.
• OUD medications can help patients reduce or stop illicit opioid use and improve their health and functioning.
• Medications should be considered for all patients with OUD. Opioid medications should be reserved for those with moderate-to-severe OUD with physical dependence.
• Patients with OUD should be informed of the risks and benefits of medications to treat OUD, treatment without medication, and no treatment.
• Patients should be advised on where and how to get treatment with OUD medication.
• Doses and schedules of medications must be individualized.

Part 4: Bringing Together Addiction Treatment Counselors, Clients, and Healthcare Professionals:

• Many patients taking OUD medication benefit from counseling as part of treatment.
• Counselors play the same role for clients with OUD who take medication as for clients with any other SUD.
• Counselors help clients recover by addressing the challenges and consequences of addiction.
• OUD is often a chronic illness requiring ongoing communication among patients and providers to ensure that patients fully benefit from both medication and psychosocial treatment and support.
• OUD medications are safe and effective when prescribed and taken appropriately.

• Medication is integral to recovery for many people with OUD. Medication usually produces better treatment outcomes than outpatient treatment without medication. • Supportive counseling environments for clients who take OUD medication can promote treatment and help build recovery capital. Part 5: Resources Related to Medications for Opioid Use Disorder: • Practice guidelines and decision-making tools can help healthcare professionals with OUD screening, assessment, diagnosis, treatment planning, and referral. • Patient- and family-oriented resources provide information about opioid addiction in general; the role of medication, behavioral and supportive services, and mutual-help groups in the treatment of OUD; how-tos for identifying recovery support services; and how-tos for locating medical and behavioral health service providers who specialize in treating OUD or other SUDs.	
Recommendation Summary	Approach to OUD treatment: There is no "one size fts all" approach to OUD treatment. Many people with OUD benefit from treatment with medication for varying lengths of time, including lifelong treatment. Ongoing outpatient medication treatment for OUD is linked to better retention and outcomes than treatment without medication. Even so, some people stop using opioids on their own; others recover through support groups or specialty outpatient or residential treatment with or without medication. Still, FDA-approved medication should be considered and offered to patients with OUD as part of their treatment. Benefits: The three FDA-approved medications used to treat OUD improve patients' health and wellness by: • Reducing or eliminating withdrawal symptoms: methadone, buprenorphine. • Blunting or blocking the effects of illicit opioids: methadone, naltrexone, buprenorphine. • Reducing or eliminating cravings to use opioids: methadone, naltrexone, buprenorphine. Effectiveness: The science demonstrating the effectiveness of medication for OUD is strong. For example, methadone, extended-release injectable naltrexone (XR-NTX), and buprenorphine were each found to be more effective in reducing illicit opioid use than no medication in randomized clinical trials, which are the gold standard for demonstrating efficacy in clinical medicine. Methadone and buprenorphine treatment have also been associated with reduced risk of overdose death. - This doesn't mean that remission and recovery occur only through medication - Medication for OUD should be successfully integrated with outpatient and residential treatment - Patients treated with OUD medications can benefit from individualized psychosocial supports Methadone retains patients in treatment and reduces illicit opioid use more effectively than placebo, medically supervised withdrawal, or no treatment, as numerous clinical trials and meta-analyses of studies conducted in many countries show. Higher methadone doses are associated with superior outcomes. Given the evidence of methadone's effectiveness, WHO lists it as an essential medication. Methadone treatment has by far the largest, oldest evidence base of all treatment approaches to opioid addiction. Naltrexone XR-NTX reduces illicit opioid use and retains patients in treatment more effectively than placebo and no medication, according to findings from randomized controlled trials. Buprenorphine in its sublingual form retains patients in treatment and reduces illicit opioid use more effectively than placebo. It also reduces HIV risk behaviors. Long-term studies of buprenorphine show its effectiveness outside of clinical research protocols. Naloxone, a short-acting opioid antagonist, is also often included in the buprenorphine formulation to help prevent diversion to injected misuse. Because of the evidence of buprenorphine's effectiveness, WHO lists it as an essential medication. Buprenorphine is available in "transmucosal" (i.e., sublingual or buccal) formulations. Buprenorphine implants can be effective in stable patients. More research is needed to establish implants' effectiveness outside of research studies, but findings to date are promising. FDA approved buprenorphine extended-release injection (Sublocade) in November 2017 to treat patients with moderate or severe OUD who have first received treatment with transmucosal buprenorphine for at least 1 week. This buprenorphine formulation is a monthly subcutaneous injection.

Assessment, Treatment, and Risk Management Assessment	Healthcare professionals, treatment providers, and policymakers have a responsibility to expand access to evidence-based, effective care for people with OUD. Screening can identify patients who may have diseases or conditions related to their substance use. Health care in general medical settings routinely includes screening for common, treatable conditions such as cancer that are associated with significant morbidity and mortality. Screening for SUDs is important, as misuse of alcohol, tobacco, and other substances is common among patients in medical settings. Screening can identify substance misuse in patients who wouldn't otherwise discuss it or connect it with the negative consequences they're experiencing. Some patients may spontaneously reveal their substance use and ask for help. The TIP expert panel recommends that healthcare professionals screen patients for alcohol, tobacco, prescription drug, and illicit drug use at least annually. Assessment: Determine the Need for and Extent of Assessment Assess patients for OUD if: • They screen positive for opioid misuse. • They disclose opioid misuse. • Signs or symptoms of opioid misuse are present. The extent of assessment depends on a provider's ability to treat patients directly. *If a provider does not offer medication*, the focus should be on medical assessment, making a diagnosis of OUD, and patient safety. *If the provider offers medication,* the patient needs more comprehensive assessment, including: • A review of the prescription drug monitoring program (PDMP). • A history, including a review of systems. • A targeted physical exam for signs of opioid withdrawal, intoxication, injection, and other medical consequences of misuse. • Determination of OUD diagnosis and severity. • Appropriate laboratory tests in addition to those recommended by the non-treating provider (e.g., urine or oral fluid drug tests, liver function tests, hepatitis B test). Take a Complete History. Staff should prioritize medical, mental health, substance use, and SUD treatment histories. Treatment Planning or Referral: Making Decisions About Treatment Start by sharing the diagnosis with patients and hearing their feedback. Patients with OUD need to make several important treatment decisions: • Whether to begin medication to treat OUD. • What type of OUD medication to take. • Where and how to access desired treatment. • Whether to access potentially beneficial mental health, recovery support, and other ancillary services, whether or not they choose medication for OUD. *Offer information to patients about the various treatments for OUD and collaborate with them to make decisions about treatment plans or referrals.* Support patient preferences for treatment settings and services. Providers should ensure that patients understand the risks and benefits of all options. Without this understanding, patients can't give truly informed consent. Preventing Opioid-Related Overdose: Every patient who misuses opioids or has OUD should receive opioid overdose prevention education and a naloxone prescription. *Patients with OUD are much more likely to die than their peers, and HIV, hepatitis C, and skin and soft tissue infections are common among this population.* Help reduce these OUD-related risks by testing patients for HIV and hepatitis and by educating patients about: • Using new syringes. • Avoiding syringe sharing. • Avoiding sharing other supplies during the injection process. • Preventing opioid overdose (see the "Preventing Opioid-Related Overdose" section). • Obtaining overdose prevention information and resources • Obtaining naloxone and instructions for its use.
Treatment Settings	Almost all healthcare settings are appropriate for screening and assessing for OUD and offering medication onsite or by referral. Settings that offer OUD treatment have expanded from specialty sites (certified OTPs, residential facilities, outpatient addiction treatment programs, and addiction specialist physicians' offices) to general primary care practices, health centers, emergency departments, inpatient medical and psychiatric units, jails and prisons, and other settings. Because of the strength of the science, a 2016 report from the Surgeon General urged adoption of medication for OUD along with recovery supports and other behavioral health services throughout the healthcare system.

Treatment Management	• Only physicians; nurse practitioners; physician assistants; and, until October 1, 2023, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives can prescribe buprenorphine for OUD. They must get a federal waiver to do so. • Only federally certified, accredited opioid treatment programs (OTPs) can dispense methadone to treat OUD. OTPs can administer and dispense buprenorphine without a federal waiver. • Any prescriber can offer naltrexone. *Important:* Before initiating OUD medication, providers should check their states' PDMPs to determine whether their patients receive prescriptions for controlled substances from other healthcare professionals. This TIP recommends ways that addiction treatment counselors can collaborate with healthcare professionals to support client-centered, trauma-informed OUD treatment and recovery.

EXHIBIT 1.2. Comparison of Medications for OUD

PRESCRIBING CONSIDERATIONS	METHADONE	NALTREXONE	BUPRENORPHINE
Mechanism of Action at mu-Opioid Receptor	Agonist	Antagonist	Partial agonist
Phase of Treatment	Medically supervised withdrawal, maintenance	Prevention of relapse to opioid misuse, following medically supervised withdrawal	Medically supervised withdrawal, maintenance
Route of Administration	Oral	Oral, intramuscular extended-release	Sublingual, buccal, subdermal implant, subcutaneous extended release injection
Possible Adverse Effects	Constipation, hyperhidrosis, respiratory depression, sedation, QT prolongation, sexual dysfunction, severe hypotension including orthostatic hypotension and syncope, misuse potential, neonatal abstinence syndrome	Nausea, anxiety, insomnia, precipitated opioid withdrawal, hepatotoxicity, vulnerability to opioid overdose, depression, suicidality, muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders **Intramuscular:** Pain, swelling, induration (including some cases requiring surgical intervention)	Constipation, nausea, precipitated opioid withdrawal, excessive sweating, insomnia, pain, peripheral edema, respiratory depression (particularly combined with benzodiazepines or other CNS depressants), misuse potential, neonatal abstinence syndrome **Implant:** Nerve damage during insertion/removal, accidental overdose or misuse if extruded, local migration or protrusion **Subcutaneous Injection:** Injection site itching or pain, death from intravenous injection
Regulations and Availability	Schedule II; only available at federally certified OTPs and the acute inpatient hospital setting for OUD treatment	Not a scheduled medication; not included in OTP regulations; requires prescription; office-based treatment or specialty substance use treatment programs, including OTPs	Schedule III; requires waiver to prescribe outside OTPs **Implant:** Prescribers must be certified in the Probuphine Risk Evaluation and Mitigation Strategy (REMS) Program. Providers who wish to insert/remove implants are required to obtain special training and certification in the REMS Program **Subcutaneous Injection:** Healthcare settings and pharmacies must be certified in the Sublocade REMS Program and only dispense the medication directly to a provider for administration

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