ASAM

THE

NATIONAL PRACTICE GUIDELINE

For the Use of Medications
in the Treatment of
Addiction Involving Opioid Use

ASAM
The Voice of Addiction Medicine
American Society of Addiction Medicine

AMERICAN SOCIETY OF ADDICTION MEDICINE
FOUNDED 1954
ASAM

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EXECUTIVE SUMMARY

Purpose

The American Society of Addiction Medicine (ASAM) developed this *National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use* to provide information on evidence-based treatment of opioid use disorder. (Hereafter, in this document, this National Practice Guideline will be referred to as "*Practice Guideline*.")

Background

Opioid use disorder is a chronic, relapsing disease, which has significant economic, personal, and public health consequences. Many readers of this *Practice Guideline* may recognize the term "opioid use disorder" as it is used in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5), developed by the American Psychiatric Association; others may be more familiar with the term "opioid dependence," as used in previous editions of the DSM.[1]

The American Society of Addiction Medicine defines addiction as "a primary, chronic disease of brain reward, motivation, memory, and related circuitry," with a "dysfunction in these circuits" being reflected in "an individual pathologically pursuing reward and/or relief by substance use and other behaviors." In this context, the preferred term by ASAM for this serious bio-psycho-social-spiritual illness would be "addiction involving opioid use." ASAM views addiction as a fundamental neurological disorder of "brain reward, motivation, memory, and related circuitry," and recognizes that there are unifying features in all cases of addiction, including substance-related addiction and nonsubstance-related addiction. It is clear that a variety of substances commonly associated with addiction work on specific receptors in the nervous system and on specific neurotransmitter systems. Specific pharmacological agents used in the

treatment of addiction exert their effects via their actions on specific receptors. Hence, the medications used in the treatment of addiction have specific efficacy based on their own molecular structure and the particular neurotransmitters affected by that medication. Medications developed for the treatment of addiction involving opioid use may have benefits in the treatment of addiction involving an individual's use of other substances. For instance, naltrexone, which is approved by the US Food and Drug Administration (FDA) for the treatment of opioid dependence using DSM, 4th Edition (DSM-IV) terminology, is also US FDA-approved for the treatment of alcohol dependence as per the DSM-IV guidelines.[2]

The American Society of Addiction Medicine recognizes that research is yet to be done to confirm the specificity of its conceptualization of addiction as a medical and a psychiatric illness. Both the American Medical Association, as noted in various policy and position statements, and the *International Classification of Diseases* (ICD), recognize addiction as both a medical and a psychiatric disorder.[3,4] ASAM encourages clinicians, researchers, educators, and policy makers to use the term ''addiction'' regardless of whether the patient's condition at a given point in its natural history seems to more prominently involve opioid use, alcohol use, nicotine use, or engagement in addictive behaviors such as gambling. Given the widespread North American application of the DSM's categorization of disorders, this *Practice Guideline* will, for the sake of brevity and convention, use the term ''opioid use disorder.''

According to the 2013 National Survey on Drug Use and Health (NSDUH), 4.5 million individuals in the United States were current (past month), nonmedical users of prescription opioids. Nonmedical use of opioids and other prescription drugs constitute hazardous and risky behavior which should be discouraged, given the potential that unauthorized use of such substances has for harm (to the user). Medication therapy related to opioids focuses not only on nonmedical use but also on an attempt to treat the medical illness, addiction. The 2013 NSDUH further found that 1.9 million persons in America met DSM-IV criteria for opioid use disorder associated with their use of prescription opioids, and that more than 0.5 million additional individuals have met DSM-IV criteria for opioid use disorder associated with their use of heroin.[5]

Opioid use is associated with increased mortality. The leading causes of death in people using opioids for nonmedical purposes are overdose and trauma.[6] The injection route use (intravenous or even intramuscular [IM]) of opioids or other drugs increases the risk of being exposed to HIV, viral hepatitis, and other infectious agents.

Scope of Guideline

This *Practice Guideline* was developed for the evaluation and treatment of opioid use disorder and for the management of opioid overdose. The medications covered in this guideline are mainly, but not exclusively, those that have been US FDA-approved for the treatment of opioid dependence, as defined in prior versions of the DSM, and not necessarily the most recent version of the manual, the DSM-5.[7] DSM-5 combined the criteria for opioid abuse and opioid dependence from prior versions of the DSM in its new

diagnosis of opioid use disorder; therefore, pharmacologic treatment may not be appropriate for all patients along the entire opioid use disorder continuum. In a study comparing opioid dependence from DSM-IV and opioid use disorder from DSM-5, optimal concordance occurred when four or more DSM-5 criteria were endorsed (ie, the DSM-5 threshold for moderate opioid use disorder).[8] Other medications have been used off-label to treat opioid use disorder (clearly noted in the text); however, the Guideline Committee has not issued recommendations on the use of those medications. As a final note related to references to medications, whether US FDA-approved or off-label, cost and/or cost effectiveness were not considerations in the development of this *Practice Guideline*.

Intended Audience

This *Practice Guideline* is primarily intended for clinicians involved in evaluating patients and providing authorization for pharmacological treatments at any level. The intended audience falls into the broad groups of physicians; other healthcare providers (especially those with prescribing authority); medical educators and faculty for other healthcare professionals in training; and clinical care managers, including those offering utilization management services.

Qualifying Statement

This ASAM *Practice Guideline* is intended to aid clinicians in their clinical decision-making and patient management. The *Practice Guideline* strives to identify and define clinical decision-making junctures that meet the needs of *most patients* in *most circumstances*. Clinical decision-making should involve consideration of the quality and availability of expertise and services in the community wherein care is provided. In circumstances in which the *Practice Guideline* is being used as the basis for regulatory or payer decisions, improvement in quality of care should be the goal. Finally, prescribed courses of treatment contained in recommendations in this *Practice Guideline* are effective only if the recommendations, as outlined, are followed. Because lack of patient understanding and adherence may adversely affect outcomes, clinicians should make every effort to promote the patient's understanding of, and adherence to, prescribed and recommended pharmacological and psychosocial treatments. Patients should be informed of the risks, benefits, and alternatives to a particular treatment, and should be an active party to shared decision-making whenever feasible. Recommendations in this *Practice Guideline* do not supersede any federal or state regulation.

Overview of Methodology

This *Practice Guideline* was developed using the RAND Corporation (RAND)/University of California, Los Angeles (UCLA) Appropriateness Method (RAM) – a process that combines scientific evidence and clinical knowledge to determine the appropriateness of a set of clinical procedures. The RAM is a deliberate approach encompassing review of existing guidelines, literature reviews, appropriateness ratings, necessity reviews, and document development. For this project, ASAM selected an independent committee to oversee guideline development, to participate in review of

treatment scenarios, and to assist in writing. ASAM's Quality Improvement Council, chaired by Margaret Jarvis, MD, oversaw the selection process for the independent development committee, referred to as the Guideline Committee.

The Guideline Committee was comprised of 10 experts and researchers from multiple disciplines, medical specialties, and subspecialties, including academic research, internal medicine, family medicine, addiction medicine, addiction psychiatry, general psychiatry, obstetrics/gynecology, pharmacology, and clinical neurobiology. Physicians with both allopathic and osteopathic training were represented in the Guideline Committee. The Guideline Committee was assisted by a technical team of researchers from the Treatment Research Institute (TRI) affiliated with the University of Pennsylvania (see page 2), and worked under the guidance of Dr. Kyle Kampman who led the TRI team as Principal Investigator in implementing the RAM.

Summary of Recommendations

Part 1: Assessment and Diagnosis of Opioid Use Disorder

Assessment Recommendations

(1) First clinical priority should be given to identifying and making appropriate referral for any urgent or emergent medical or psychiatric problem(s), including drug-related impairment or overdose.

(2) Completion of the patient's medical history should include screening for concomitant medical conditions, including infectious diseases (hepatitis, HIV, and tuberculosis [TB]), acute trauma, and pregnancy.

(3) A physical examination should be completed as a component of the comprehensive assessment process. The prescriber (the clinician authorizing the use of a medication for the treatment of opioid use disorder) may conduct this physical examination him/herself, or, in accordance with the ASAM Standards, ensure that a current physical examination is contained within the patient medical record before a patient is started on a new medication for the treatment of his/her addiction.

(4) Initial laboratory testing should include a complete blood count, liver function tests, and tests for hepatitis C and HIV. Testing for TB and sexually transmitted infections should also be considered. Hepatitis B vaccination should be offered, if appropriate.

(5) The assessment of women presents special considerations regarding their reproductive health. Women of childbearing age should be tested for pregnancy, and all women of childbearing potential and age should be queried regarding methods of contraception, given the increase in fertility that results from effective opioid use disorder treatment.

(6) Patients being evaluated for addiction involving opioid use, and/or for possible medication use in the treatment of opioid use disorder, should undergo (or have completed) an assessment of mental health status and possible psychiatric disorders (as outlined in the ASAM Standards).

(7) Opioid use is often co-occurring with other substance-related disorders. An evaluation of past and current substance use and a determination of the totality of substances that surround the addiction should be conducted.

(8) The use of marijuana, stimulants, or other addictive drugs should not be a reason to suspend opioid use disorder treatment. However, evidence demonstrates that patients who are actively using substances during opioid use disorder treatment have a poorer prognosis. The use of benzodiazepines and other sedative hypnotics may be a reason to suspend agonist treatment because of safety concerns related to respiratory depression.

(9) A tobacco use query and counseling on cessation of tobacco products and electronic nicotine delivery devices should be completed routinely for all patients, including those who present for evaluation and treatment of opioid use disorder.

(10) An assessment of social and environmental factors should be conducted (as outlined in the ASAM Standards) to identify facilitators and barriers to addiction treatment, and specifically to pharmacotherapy. Before a decision is made to initiate a course of pharmacotherapy for the patient with opioid use disorder, the patient should receive a multidimensional assessment in fidelity with *The ASAM Criteria: Treatment Criteria for Addictive, Substance-Related, and Co-occuring Conditions* (the "ASAM Criteria"). Addiction should be considered a bio-psycho-social-spiritual illness, for which the use of medication(s) is but only one component of overall treatment.

Diagnosis Recommendations

(1) Other clinicians may diagnose opioid use disorder, but confirmation of the diagnosis by the provider with prescribing authority, and who recommends medication use, must be obtained before pharmacotherapy for opioid use disorder commences.

(2) Opioid use disorder is primarily diagnosed on the basis of the history provided by the patient and a comprehensive assessment that includes a physical examination.

(3) Validated clinical scales that measure withdrawal symptoms, for example, the Objective Opioid Withdrawal Scale (OOWS), the Subjective Opioid Withdrawal Scale (SOWS), and the Clinical Opioid Withdrawal Scale (COWS), may be used to assist in the evaluation of patients with opioid use disorder.

(4) Urine drug testing during the comprehensive assessment process, and frequently during treatment, is recommended. The frequency of drug testing is determined by a number of factors including the stability of the patient, the type of treatment, and the treatment setting.

Part 2: Treatment Options

(1) The choice of available treatment options for addiction involving opioid use should be a shared decision between clinician and patient.

(2) Clinicians should consider the patient's preferences, past treatment history, and treatment setting when deciding between the use of methadone, buprenorphine, and naltrexone in the treatment of addiction involving opioid use. The treatment setting described as level 1 treatment in the

ASAM Criteria may be a general outpatient location such as a clinician's practice site. The setting described as level 2 in the ASAM Criteria may be an intensive outpatient treatment or partial hospitalization program housed in a specialty addiction treatment facility, a community mental health center, or another setting. The ASAM Criteria describes level 3 or level 4 treatment, respectively, as a residential addiction treatment facility or hospital.

(3) The venue in which treatment is provided is as important as the specific medication selected. Opioid treatment programs (OTPs) offer daily supervised dosing of methadone, and increasingly of buprenorphine. In accordance with the Federal law (21 CFR §1306.07), office-based opioid treatment (OBOT), which provides medication on a prescribed weekly or monthly basis, is limited to buprenorphine.[9] Naltrexone can be prescribed in any setting by any clinician with the authority to prescribe any medication. Clinicians should consider a patient's psychosocial situation, co-occurring disorders, and risk of diversion when determining whether OTP or OBOT is most appropriate.

(4) OBOT may not be suitable for patients with active alcohol use disorder or sedative, hypnotic, or anxiolytic use disorder (or who are in the treatment of addiction involving the use of alcohol or other sedative drugs, including benzodiazepines or benzodiazepine receptor agonists). It may also be unsuitable for persons who are regularly using alcohol or other sedatives, but do not have addiction or a specific substance use disorder related to that class of drugs. The prescribing of benzodiazepines or other sedative-hypnotics should be used with extreme caution in patients who are prescribed methadone or buprenorphine for the treatment of an opioid use disorder.

(5) Methadone is recommended for patients who may benefit from daily dosing and supervision in an OTP, or for patients for whom buprenorphine for the treatment of opioid use disorder has been used unsuccessfully in an OTP or OBOT setting.

(6) Oral naltrexone for the treatment of opioid use disorder is often adversely affected by poor medication adherence. Clinicians should reserve its use for patients who would be able to comply with special techniques to enhance their adherence, for example, observed dosing. Extended-release injectable naltrexone reduces, but does not eliminate, issues with medication adherence.

Part 3: Treating Opioid Withdrawal

(1) Using medications for opioid withdrawal management is recommended over abrupt cessation of opioids. Abrupt cessation of opioids may lead to strong cravings, which can lead to continued use.

(2) Patients should be advised about risk of relapse and other safety concerns from using opioid withdrawal management as standalone treatment for opioid use disorder. Opioid withdrawal management on its own is not a treatment method.

(3) Assessment of a patient undergoing opioid withdrawal management should include a thorough medical history and physical examination, focusing on signs and symptoms associated with opioid withdrawal.

(4) Opioid withdrawal management in cases in which methadone is used to manage withdrawal symptoms must be done in an inpatient setting or in an OTP. For short-acting opioids, tapering schedules that decrease in daily doses of prescribed methadone should begin with doses between 20 and 30 mg per day, and should be completed within 6–10 days.

(5) Opioid withdrawal management in cases in which buprenorphine is used to manage withdrawal symptoms should not be initiated until 12–18 hours after the last dose of a short-acting agonist such as heroin or oxycodone, and 24–48 hours after the last dose of a long-acting agonist such as methadone. A dose of buprenorphine sufficient to suppress withdrawal symptoms is given (this can be 4–16 mg per day) and then the dose is tapered. The duration of the tapering schedule can be as brief as 3–5 days or as long as 30 days or more.

(6) The use of combinations of buprenorphine and low doses of oral naltrexone to manage withdrawal and facilitate the accelerated introduction of extended-release injectable naltrexone has shown promise. More research will be needed before this can be accepted as standard practice.

(7) The Guideline Committee recommends, based on consensus opinion, the inclusion of clonidine as a practice to support opioid withdrawal. Clonidine is not US FDA-approved for the treatment of opioid withdrawal, but it has been extensively used off-label for this purpose. Clonidine may be used orally or transdermally at doses of 0.1–0.3 mg every 6–8 hours, with a maximum dose of 1.2 mg daily, to assist in the management of opioid withdrawal symptoms. Its hypotensive effects often limit the amount that can be used. Clonidine can be combined with other non-narcotic medications targeting specific opioid withdrawal symptoms such as benzodiazepines for anxiety, loperamide for diarrhea, acetaminophen or non-steroidal anti-inflammatory medications (NSAIDs) for pain, and ondansetron or other agents for nausea.

(8) Opioid withdrawal management using anesthesia UROD is not recommended due to high risk for adverse events or death. Naltrexone-facilitated opioid withdrawal management can be a safe and effective approach, but should be used only by clinicians experienced with this clinical method, and in cases in which anesthesia or conscious sedation are not being employed.

Part 4: Methadone

(1) Methadone is a treatment option recommended for patients who are physiologically dependent on opioids, able to give informed consent, and who have no specific contraindications for agonist treatment when it is prescribed in the context of an appropriate plan that includes psychosocial intervention.

(2) The recommended initial dose for methadone ranges from 10 to 30 mg, with reassessment in 3–4 hours, and a second dose not to exceed 10 mg on the first day if withdrawal symptoms are persisting.

(3) The usual daily dosage of methadone ranges from 60 to 120 mg. Some patients may respond to lower doses and some patients may need higher doses. Dosage increases

in 5–10-mg increments applied no more frequently than every 7 days (depending on clinical response) are necessary to avoid oversedation, toxicity, or even iatrogenic overdose deaths.

(4) The administration of methadone should be monitored because unsupervised administration can lead to misuse and diversion. OTP regulations require monitored medication administration until the patient's clinical response, and behavior demonstrates that the prescribing of nonmonitored doses is appropriate.

(5) Psychosocial treatment, though sometimes minimally needed, should be implemented in conjunction with the use of methadone in the treatment of opioid use disorder.

(6) Methadone should be reinstituted immediately if relapse occurs, or when an assessment determines that the risk of relapse is high for patients who previously received methadone in the treatment of opioid use disorder, but who are no longer prescribed such treatment.

(7) Strategies directed at relapse prevention are an important part of comprehensive addiction treatment and should be included in any plan of care for a patient receiving active opioid treatment or ongoing monitoring of the status of their addictive disease.

(8) Switching from methadone to another medication for the treatment of opioid use disorder may be appropriate if the patient experiences intolerable side effects or is not successful in attaining or maintaining treatment goals through the use of methadone.

(9) Patients switching from methadone to buprenorphine in the treatment of opioid use disorder should be on low doses of methadone before switching medications. Patients on low doses of methadone (30–40 mg per day or less) generally tolerate transition to buprenorphine with minimal discomfort, whereas patients on higher doses of methadone may experience significant discomfort in switching medications.

(10) Patients switching from methadone to oral naltrexone or extended-release injectable naltrexone must be completely withdrawn from methadone and other opioids, before they can receive naltrexone. The only exception would apply when an experienced clinician receives consent from the patient to embark on a plan of naltrexone-facilitated opioid withdrawal management.

(11) Patients who discontinue agonist therapy with methadone or buprenorphine and then resume opioid use should be made aware of the risks associated with opioid overdose, and especially the increased risk of death.

Part 5: Buprenorphine

(1) Opioid-dependent patients should wait until they are experiencing mild to moderate opioid withdrawal before taking the first dose of buprenorphine to reduce the risk of precipitated withdrawal. Generally, buprenorphine initiation should occur at least 6–12 hours after the last use of heroin or other short-acting opioids, or 24–72 hours after their last use of long-acting opioids such as methadone.

(2) Induction of buprenorphine should start with a dose of 2–4 mg. Dosages may be increased in increments of 2–4 mg.

(3) Clinicians should observe patients in their offices during induction. Emerging research, however, suggests that many patients need ''not'' be observed and that home buprenorphine induction may be considered. Home-based induction is recommended only if the patient or prescribing physician is experienced with the use of buprenorphine. This is based on the consensus opinion of the Guideline Committee.

(4) Buprenorphine doses after induction and titration should be, on average, at least 8 mg per day. However, if patients are continuing to use opioids, consideration should be given to increasing the dose by 4–8 mg (daily doses of 12–16 mg or higher). The US FDA approves dosing to a limit of 24 mg per day, and there is limited evidence regarding the relative efficacy of higher doses. In addition, the use of higher doses may increase the risk of diversion.

(5) Psychosocial treatment should be implemented in conjunction with the use of buprenorphine in the treatment of opioid use disorder.

(6) Clinicians should take steps to reduce the chance of buprenorphine diversion. Recommended strategies include frequent office visits (weekly in early treatment), urine drug testing, including testing for buprenorphine and metabolites, and recall visits for pill counts.

(7) Patients should be tested frequently for buprenorphine, other substances, and prescription medications. Accessing Prescription Drug Monitoring Program (PDMP) data may be useful for monitoring.

(8) Patients should be seen frequently at the beginning of their treatment. Weekly visits (at least) are recommended until patients are determined to be stable. There is no recommended time limit for treatment.

(9) Buprenorphine taper and discontinuation is a slow process and close monitoring is recommended. Buprenorphine tapering is generally accomplished over several months. Patients should be encouraged to remain in treatment for ongoing monitoring past the point of discontinuation.

(10) When considering a switch from buprenorphine to naltrexone, 7–14 days should elapse between the last dose of buprenorphine and the start of naltrexone to ensure that the patient is not physically dependent on opioids before starting naltrexone.

(11) When considering a switch from buprenorphine to methadone, there is no required time delay because the addition of a full mu-opioid agonist to a partial agonist does not typically result in any type of adverse reaction.

(12) Patients who discontinue agonist therapy and resume opioid use should be made aware of the risks associated with an opioid overdose, and especially the increased risk of death.

Part 6: Naltrexone

(1) Naltrexone is a recommended treatment in preventing relapse in opioid use disorder. Oral formula naltrexone may be considered for patients in whom adherence can be supervised or enforced. Extended-release injectable naltrexone may be more suitable for patients who have issues with adherence.

(2) Oral naltrexone should be taken daily in 50-mg doses, or three times weekly in two 100-mg doses followed by one 150-mg dose.

(3) Extended-release injectable naltrexone should be administered every 4 weeks by deep IM injection in the gluteal muscle at a set dosage of 380 mg per injection.

(4) Psychosocial treatment is recommended in conjunction with treatment with naltrexone. The efficacy of naltrexone use in conjunction with psychosocial treatment has been established, whereas the efficacy of extended-release injectable naltrexone without psychosocial treatment ''has not'' been established.

(5) There is no recommended length of treatment with oral naltrexone or extended-release injectable naltrexone. Duration depends on clinical judgment and the patient's individual circumstances. Because there is no physical dependence associated with naltrexone, it can be stopped abruptly without withdrawal symptoms.

(6) Switching from naltrexone to methadone or buprenorphine should be planned, considered, and monitored. Switching from an antagonist such as naltrexone to a full agonist (methadone) or a partial agonist (buprenorphine) is generally less complicated than switching from a full or partial agonist to an antagonist because there is no physical dependence associated with antagonist treatment and thus no possibility of precipitated withdrawal. Patients being switched from naltrexone to buprenorphine or methadone will not have physical dependence on opioids and thus the initial doses of methadone or buprenorphine used should be low. Patients should not be switched until a significant amount of the naltrexone is no longer in their system, about 1 day for oral naltrexone or 30 days for extended-release injectable naltrexone.

(7) Patients who discontinue antagonist therapy and resume opioid use should be made aware of the increased risks associated with an opioid overdose, and especially the increased risk of death.

Part 7: Psychosocial Treatment in Conjunction With Medications for the Treatment of Opioid Use Disorder

(1) Psychosocial treatment is recommended in conjunction with any pharmacological treatment of opioid use disorder. At a minimum, psychosocial treatment should include the following: psychosocial needs assessment, supportive counseling, links to existing family supports, and referrals to community services.

(2) Treatment planning should include collaboration with qualified behavioral healthcare providers to determine the optimal type and intensity of psychosocial treatment and for renegotiation of the treatment plan for circumstances in which patients do not adhere to recommended plans for, or referrals to, psychosocial treatment.

(3) Psychosocial treatment is generally recommended for patients who are receiving opioid agonist treatment (methadone or buprenorphine).

(4) Psychosocial treatment should be offered with oral and extended-release injectable naltrexone. The efficacy of extended-release injectable naltrexone to treat opioid use

disorder has not been confirmed when it has been used as pharmacotherapy without accompanying psychosocial treatment.

Part 8: Special Populations: Pregnant Women

(1) The first priority in evaluating pregnant women for opioid use disorder should be to identify emergent or urgent medical conditions that require immediate referral for clinical evaluation.

(2) A medical examination and psychosocial assessment is recommended when evaluating pregnant women for opioid use disorder.

(3) Obstetricians and gynecologists should be alert to signs and symptoms of opioid use disorder. Pregnant women with opioid use disorder are more likely to seek prenatal care late in pregnancy, miss appointments, experience poor weight gain, or exhibit signs of withdrawal or intoxication.

(4) Psychosocial treatment is recommended in the treatment of pregnant women with opioid use disorder.

(5) Counseling and testing for HIV should be provided in accordance with state law. Tests for hepatitis B and C and liver function are also suggested. Hepatitis A and B vaccination is recommended for those whose hepatitis serology is negative.

(6) Urine drug testing may be used to detect or confirm suspected opioid and other drug use with informed consent from the mother, realizing that there may be adverse legal and social consequences of her use. State laws differ on reporting substance use during pregnancy. Laws that penalize women for use and for obtaining treatment serve to prevent women from obtaining prenatal care and worsen outcomes.

(7) Pregnant women who are physically dependent on opioids should receive treatment using methadone or buprenorphine monoproduct rather than withdrawal management or abstinence.

(8) Care for pregnant women with opioid use disorder should be comanaged by an obstetrician and an addiction specialist physician. Release of information forms need to be completed to ensure communication among healthcare providers.

(9) Treatment with methadone should be initiated as early as possible during pregnancy.

(10) Hospitalization during initiation of methadone and treatment with buprenorphine may be advisable due to the potential for adverse events, especially in the third trimester.

(11) In an inpatient setting, methadone should be initiated at a dose range of 20–30 mg. Incremental doses of 5–10 mg are given every 3–6 hours, as needed, to treat withdrawal symptoms.

(12) After induction, clinicians should increase the methadone dose in 5–10-mg increments per week. The goal is to maintain the lowest dose that controls withdrawal symptoms and minimizes the desire to use additional opioids.

(13) Twice daily dosing is more effective and has fewer side effects than single dosing, but may not be practical because methadone is typically dispensed in an outpatient clinic.

(14) Clinicians should be aware that the pharmacokinetics of methadone are affected by pregnancy. With advancing gestational age, plasma levels of methadone progressively decrease and clearance increases. Increased or split doses may be needed as pregnancy progresses. After child birth, doses may need to be adjusted.

(15) Buprenorphine monoproduct is a reasonable and recommended alternative to methadone for pregnant women. Whereas there is evidence of safety, there is insufficient evidence to recommend the combination buprenorphine/naloxone formulation.

(16) If a woman becomes pregnant while she is receiving naltrexone, it is appropriate to discontinue the medication if the patient and doctor agree that the risk of relapse is low. If the patient is highly concerned about relapse and wishes to continue naltrexone, she should be informed about the risks of staying on naltrexone and provide her consent for ongoing treatment. If the patient wishes to discontinue naltrexone, but then reports relapse to opioid use, it may be appropriate to consider treatment with methadone or treatment with buprenorphine.

(17) Naloxone is not recommended for use in pregnant women with opioid use disorder except in situations of life-threatening overdose.

(18) Mothers receiving methadone and buprenorphine monoproduct for the treatment of opioid use disorders should be encouraged to breastfeed.

Part 9: Special Populations: Individuals With Pain

(1) For all patients with pain, it is important that the correct diagnosis be made and that a target suitable for treatment is identified.

(2) If pharmacological treatment is considered, non-narcotic medications such as acetaminophen and NSAIDs should be tried first.

(3) Opioid agonists (methadone or buprenorphine) should be considered for patients with active opioid use disorder who are not under treatment.

(4) Pharmacotherapy in conjunction with psychosocial treatment should be considered for patients with pain who have opioid use disorder.

(5) Patients on methadone for the treatment of opioid use disorder will require doses of opioids in addition to their regular daily dose of methadone to manage acute pain.

(6) Patients on methadone for the treatment of opioid use disorder and who are admitted for surgery may require additional short-acting opioid pain relievers. The dose of pain relievers prescribed may be higher due to tolerance.

(7) Temporarily increasing buprenorphine dosing may be effective for mild acute pain.

(8) For severe acute pain, discontinuing buprenorphine and commencing on a high-potency opioid (such as fentanyl) is advisable. Patients should be monitored closely and additional interventions such as regional anesthesia should also be considered.

(9) The decision to discontinue buprenorphine before an elective surgery should be made in consultation with the attending surgeon and anesthesiologist. If it is decided that buprenorphine should be discontinued before surgery, this should occur 24–36 hours in advance of surgery and restarted postoperatively when the need for full opioid agonist analgesia has passed.

(10) Patients on naltrexone will not respond to opioid analgesics in the usual manner. Therefore, it is recommended that mild pain be treated with NSAIDs, and moderate to severe pain be treated with ketorolac on a short-term basis.

(11) Oral naltrexone should be discontinued 72 hours before surgery and extended-release injectable naltrexone should be discontinued 30 days before an anticipated surgery.

Part 10: Special Populations: Adolescents

(1) Clinicians should consider treating adolescents who have opioid use disorder using the full range of treatment options, including pharmacotherapy.

(2) Opioid agonists (methadone and buprenorphine) and antagonists (naltrexone) may be considered for treatment of opioid use disorder in adolescents. Age is a consideration in treatment, and Federal laws and US FDA approvals need to be considered for patients under age 18.

(3) Psychosocial treatment is recommended in the treatment of adolescents with opioid use disorder.

(4) Concurrent practices to reduce infection (eg, sexual risk reduction interventions) are recommended as components of comprehensive treatment for the prevention of sexually transmitted infections and blood-borne viruses.

(5) Adolescents may benefit from treatment in specialized treatment facilities that provide multidimensional services.

Part 11: Special Populations: Individuals With Co-occurring Psychiatric Disorders

(1) A comprehensive assessment including determination of mental health status should evaluate whether the patient is stable. Patients with suicidal or homicidal ideation should be referred immediately for treatment and possibly hospitalization.

(2) Management of patients at risk for suicide should include: reducing immediate risk; managing underlying factors associated with suicidal intent; and monitoring and follow-up.

(3) All patients with psychiatric disorders should be asked about suicidal ideation and behavior. Patients with a history of suicidal ideation or attempts should have opioid use disorder, and psychiatric medication use, monitored.

(4) Assessment for psychiatric disorder should occur at the onset of agonist or antagonist treatment. Reassessment using a detailed mental status examination should occur after stabilization with methadone, buprenorphine, or naltrexone.

(5) Pharmacotherapy in conjunction with psychosocial treatment should be considered for patients with opioid use disorder and a co-occurring psychiatric disorder.

(6) Clinicians should be aware of potential interactions between medications used to treat co-occurring psychiatric conditions and opioid use disorder.

(7) Assertive community treatment should be considered for patients with co-occurring schizophrenia and opioid use disorder who have a recent history of, or are at risk of, repeated hospitalization or homelessness.

Part 12: Special Populations: Individuals in the Criminal Justice System

(1) Pharmacotherapy for the continued treatment of opioid use disorders, or the initiation of pharmacotherapy, has been shown to be effective and is recommended for prisoners and parolees regardless of the length of their sentenced term.

(2) Individuals with opioid use disorder who are within the criminal justice system should be treated with some type of pharmacotherapy in addition to psychosocial treatment.

(3) Opioid agonists (methadone and buprenorphine) and antagonists (naltrexone) may be considered for treatment. There is insufficient evidence to recommend any one treatment as superior to another for prisoners or parolees.

(4) Pharmacotherapy should be initiated a minimum of 30 days before release from prison.

Part 13: Naloxone for the Treatment of Opioid Overdose

(1) Naloxone should be given in case of opioid overdose.

(2) Naloxone can and should be administered to pregnant women in cases of overdose to save the mother's life.

(3) The Guideline Committee, based on consensus opinion, recommends that patients who are being treated for opioid use disorder and their family members/significant others be given prescriptions for naloxone. Patients and family members/significant others should be trained in the use of naloxone in overdose.

(4) The Guideline Committee, based on consensus opinion, recommends that first responders such as emergency medical services personnel, police officers, and firefighters be trained in and authorized to administer naloxone.

Abbreviations and Acronyms

AA   Alcoholics Anonymous
ACT   Assertive Community Treatment
AIDS   Acquired Immunodeficiency Syndrome
ASAM   American Society of Addiction Medicine
CBT   Cognitive Behavioral Therapy
CDC   Centers for Disease Control
COWS   Clinical Opioid Withdrawal Scale
DATA 2000   Drug Addiction Treatment Act of 2000
DEA   Drug Enforcement Agency
DSM-III   Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition
DSM-IV   Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-5   Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG   Electrocardiogram
EMS   Emergency Medical Services
FDA   Food and Drug Administration
HBV   Hepatitis B Virus
HCV   Hepatitis C Virus
HIV   Human Immunodeficiency Virus

IDU   Injection Drug Use
IM   Intramuscular
IV   Intravenous
NA   Narcotics Anonymous
NAS   Neonatal Abstinence Syndrome
NSAIDs   Nonsteroidal Anti-inflammatory Drugs
NSDUH   National Survey on Drug Use and Health
OBOT   Office-Based Opioid Treatment
OOWS   Objective Opioid Withdrawal Scale
OTP   Opioid Treatment Program
PMDP   Prescription Drug Monitoring Program
RCT   Randomized Clinical Trial
RAM   RAND/UCLA Appropriateness Method
SAMHSA   Substance Abuse and Mental Health Services Administration
SMART   Self-Management and Recovery Therapy
SOWS   Subjective Opioid Withdrawal Scale
TB   Tuberculosis
UROD   Ultrarapid Opioid Detoxification

National Practice Guideline Glossary

Abstinence: Intentional and consistent restraint from the pathological pursuit of reward and/or relief that involves the use of substances and other behaviors. These behaviors may involve, but are not necessarily limited to, gambling, video gaming, spending, compulsive eating, compulsive exercise, or compulsive sexual behaviors.[4]

Abuse: This term is not recommended for use in clinical or research contexts. Harmful use of a specific psychoactive substance. When used to mean ''substance abuse,'' this term also applies to one category of psychoactive substance-related disorders in previous editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM). While recognizing that ''abuse'' is part of past diagnostic terminology, ASAM recommends that an alternative term be found for this purpose because of the pejorative connotations of the word ''abuse.''[4]

Addiction: Addiction is a primary, chronic disease of brain reward, motivation, memory, and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social, and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.

Addiction is characterized by inability to consistently abstain, impairment in behavioral control, cravings, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.[4]

Addiction specialist physician: Addiction specialist physicians include addiction medicine physicians and addiction psychiatrists who hold either a board certification in addiction medicine from the American Board of Addiction Medicine, a subspecialty board certification in addiction psychiatry from the American Board of Psychiatry and Neurology, a subspecialty board certification in addiction medicine from the American Osteopathic Association, or

certification in addiction medicine from the American Society of Addiction Medicine.[10]

Adherence (see also compliance): To "adhere" is "to cling, cleave (to be steadfast, hold fast), to stick fast" (Webster's Dictionary). Adherence is a term that health professionals have been using increasingly to replace the term "compliance." Both terms have been used, sometimes interchangeably, to refer to how closely patients cooperate with, follow, and take personal responsibility for the implementation of their treatment plans. The terms are often used with the more narrow sense of how well patients accomplish the goal of persistently taking medications, and also refer more broadly to all components of treatment. Assessment of patients' efforts to accomplish the goals of a treatment plan is essential to treatment success. These efforts occur along a complex spectrum from independent proactive commitment, to mentored collaboration, to passive cooperation, to reluctant partial agreement, to active resistance, and to full refusal. Attempts to understand factors that promote or inhibit adherence/compliance must take into account behaviors, attitudes, willingness, and varying degrees of capacity and autonomy. The term "adherence" emphasizes the patient's collaboration and participation in treatment. It contributes to a greater focus on motivational enhancement approaches that engage and empower patients.[4]

Adolescence: The American Academy of Pediatrics categorizes adolescence as the totality of three developmental stages – puberty to adulthood – which occur generally between 11 and 21 years of age.[11]

Agonist medication: See Opioid Agonist Medication.

Antagonist medication: See Opioid Antagonist Medication.

ASAM Criteria dimensions: The ASAM Patient Placement Criteria use six dimensions to create a holistic biopsychosocial assessment of an individual to be used for service planning and treatment. Dimension one is acute intoxication or withdrawal potential. Dimension two is biomedical conditions and conditions. Dimension three is emotional, behavioral, or cognitive conditions or complications. Dimension four is readiness for change. Dimension five is continued use or continued problem potential. Dimension six is recovery/living environment.[4]

Assertive community treatment: An evidence-based, outreach-oriented, service delivery model for people with severe and persistent mental illnesses that uses a team-based model to provide comprehensive and flexible treatment.[12]

Clinician: A health professional, such as a physician, psychiatrist, psychologist, or nurse, involved in clinical practice, as distinguished from one specializing in research.[4]

Cognitive behavioral therapy: An evidence-based psychosocial intervention that seeks to modify harmful beliefs and maladaptive behaviors, and help patients recognize, avoid, and cope with the situations in which they are most likely to misuse drugs.[13]

Co-occurring disorders: Concurrent substance use and mental disorders. Other terms used to describe co-occurring disorders include "dual diagnosis," "dual disorders," "mentally ill chemically addicted" (MICA), "chemically addicted mentally ill" (CAMI), "mentally ill substance abusers" (MISA), "mentally ill chemically dependent" (MICD), "concurrent disorders," "coexisting disorders," "comorbid disorders," and "individuals with co-occurring psychiatric and substance symptomatology" (ICOPSS). Use of the term carries no implication as to which disorder is primary and which secondary, which disorder occurred first, or whether one disorder caused the other.[4]

Compliance: See also Adherence. "To comply" is "to act in accordance with another's wishes, or with rules and regulations" (Webster's Dictionary). The term "compliance" is falling into disuse because patient engagement and responsibility to change is a goal beyond passive compliance. Given the importance of shared decision-making to improve collaboration and outcomes, patients are encouraged to actively participate in treatment decisions and take responsibility for their treatment, rather than to passively comply.[4]

Concomitant conditions: Medical conditions (eg, HIV, cardiovascular disease) and/or psychiatric conditions (eg, depression, schizophrenia) that occur along with a substance use disorder.[14]

Contingency management: An evidence-based psychosocial intervention in which patients are given tangible rewards to reinforce positive behaviors such as abstinence. Also referred to as motivational incentives.[13]

Dependence: Used in three different ways: physical dependence is a state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist; psychological dependence is a subjective sense of need for a specific psychoactive substance, either for its positive effects or to avoid negative effects associated with its abstinence; and one category of psychoactive substance use disorder in previous editions of the DSM, but not in DSM-5.[4]

Detoxification: Usually used to refer to a process of withdrawing a person from a specific psychoactive substance in a safe and effective manner. The term actually encompasses safe management of intoxication states (more literally, "detoxification") and of withdrawal states. In this document, this term has been replaced by the term Withdrawal Management.[4]

Failure (as in treatment failure): This term is not recommended for use in clinical or research contexts. Lack of progress and/or regression at any given level of care. Such a situation warrants a reassessment of the treatment plan, with modification of the treatment approach. Such situations may require changes in the treatment plan at the same level of care or transfer to a different (more or less intensive) level of care to achieve a better therapeutic response and outcome. Sometimes used to describe relapse after a single treatment episode – an inappropriate construct in describing a chronic disease or disorder. The use of "treatment failure" is therefore not a recommended concept or term to be used.[4]

Harm reduction: A treatment and prevention approach that encompasses individual and public health needs, aiming to decrease the health and socioeconomic costs and consequences of addiction-related problems, especially medical complications and transmission of infectious diseases,

without necessarily requiring abstinence. Abstinence-based treatment approaches are themselves a part of comprehensive harm reduction strategies. A range of recovery activities may be included in every harm reduction strategy.[4]

Induction (office and home): The phase of opioid treatment during which maintenance medication dosage levels are adjusted until a patient attains stabilization. Buprenorphine induction may take place in an office-based setting or home-based setting. Methadone induction must take place in an opioid treatment program (OTP).[15]

Illicit opioid (nonmedical drug use): Use of an illicit drug or the use of a prescribed medicine for reasons other than the reasons intended by the prescriber, for example, to produce positive reward or negative reward. Nonmedical use of prescription drugs often includes use of a drug in higher doses than authorized by the prescriber or through a different route of administration than intended by the prescriber, and for a purpose other than the indication intended by the prescriber (e.g. the use of methylphenidate prescribed for attention deficit hyperactivity disorder [ADHD] to produce euphoria rather than to reduce symptoms or dysfunction from ADHD).[16]

Maintenance treatment(s): Pharmacotherapy on a consistent schedule for persons with addiction, usually with an agonist or partial agonist, which mitigates against the pathological pursuit of reward and/or relief and allows remission of overt addiction-related problems.

Maintenance treatments of addiction are associated with the development of a pharmacological steady state in which receptors for addictive substances are occupied, resulting in relative or complete blockade of central nervous system receptors such that addictive substances are no longer sought for reward and/or relief. Maintenance treatments of addiction are also designed to mitigate against the risk of overdose. Depending on the circumstances of a given case, a care plan including maintenance treatments can be time-limited or can remain in place lifelong. Integration of pharmacotherapy via maintenance treatments with psychosocial treatment generally is associated with the best clinical results. Maintenance treatments can be part of an individual's treatment plan in abstinence-based recovery activities or can be a part of harm reduction strategies.[4]

Moderation management: Moderation management (MM) is a behavioral change program and national support group network for people concerned about their drinking and who desire to make positive lifestyle changes. MM empowers individuals to accept personal responsibility for choosing and maintaining their own path, whether moderation or abstinence. MM promotes early self-recognition of risky drinking behavior, when moderate drinking is a more easily achievable goal.[17]

Motivational interviewing:

(1) *Layperson's definition:* A collaborative conversation style for strengthening a person's own motivation and commitment to change.
(2) *Practitioner's definition:* A person-centered counseling style for addressing the common problem of ambivalence about change.
(3) *Technical definition:* A collaborative, goal-oriented style of communication with particular attention to the

language of change. It is designed to strengthen personal motivation for and commitment to a specific goal by eliciting and exploring the person's own reasons for change within an atmosphere of acceptance and compassion.[4]

Naloxone challenge: Naloxone is a short-acting opioid antagonist. Naloxone challenge is a test in which naloxone is administered to patients to evaluate their level of opioid dependence before the commencement of opioid pharmacotherapy.[15,18]

Naltrexone-facilitated opioid withdrawal management: This is a method of withdrawal management. It involves the use of a single dose of buprenorphine combined with multiple small doses of naltrexone over a several day period to manage withdrawal and facilitate the initiation of treatment with naltrexone.[19]

Narcotic drugs: Legally defined by the Controlled Substances Act in the United States since its enactment in 1970. The term "narcotic" is broad and can include drugs produced directly or indirectly by extraction from substances of vegetable origin, or independently by means of chemical synthesis, or by a combination of extraction and chemical synthesis. The main compounds defined as narcotics in the United States include: opium, opiates, derivatives of opium and opiates, including their isomers, esters, ethers, salts, and salts of isomers, esters, ethers (but not the isoquinoline alkaloids of opium), poppy straw and concentrate of poppy straw, coca leaves, cocaine, its salts, optical and geometric isomers, and salts of isomers and ecgonine, its derivatives, their salts, isomers, and salts of isomers. Any compound, mixture, or preparation which contains any quantity of any of the substances referred to above.[20]

Neuroadaption: See "Tolerance" for the definition.

Office-based opioid treatment (OBOT): Physicians in private practices or a number of types of public sector clinics can be authorized to prescribe outpatient supplies of the partial opioid agonist buprenorphine. There is no regulation *per se* of the clinic site itself, but of the individual physician who prescribes buprenorphine.[4]

Opiate: One of a group of alkaloids derived from the opium poppy *(Papaver somniferum)*, with the ability to induce analgesia, euphoria, and, in higher doses, stupor, coma, and respiratory depression. The term excludes synthetic opioids.[18]

Opioid: A current term for any psychoactive chemical that resembles morphine in pharmacological effects, including opiates and synthetic/semisynthetic agents that exert their effects by binding to highly selective receptors in the brain where morphine and endogenous opioids affect their actions.[16]

Opioid agonist medication: Opioid agonist medications pharmacologically occupy opioid receptors in the body. They thereby relieve withdrawal symptoms and reduce or extinguish cravings for opioids.[4]

Opioid antagonist medication: Opioid antagonist medications pharmacologically occupy opioid receptors in the body, but do not activate the receptors. This effectively blocks the receptor, preventing the brain from responding to opioids. The result is that further use of opioids does not produce euphoria or intoxication.[4]

Opioid intoxication: A condition that follows the administration of opioids, resulting in disturbances in the level

of consciousness, cognition, perception, judgment, affect, behavior, or other psychophysiological functions and responses. These disturbances are related to the acute pharmacological effects of, and learned responses to, opioids. With time, these disturbances resolve, resulting in complete recovery, except when tissue damage or other complications have arisen. Intoxication depends on the type and dose of opioid, and is influenced by factors such as an individual's level of tolerance. Individuals often take drugs in the quantity required to achieve a desired degree of intoxication. Behavior resulting from a given level of intoxication is strongly influenced by cultural and personal expectations about the effects of the drug. According to the International Classifications of Diseases-10 (ICD-10), acute intoxication is the term used for intoxication of clinical significance (F11.0). Complications may include trauma, inhalation of vomitus, delirium, coma, and convulsions, depending on the substance and method of administration.[18]

Opioid treatment program (OTP): A program certified by the United States, Substance Abuse and Mental Health Services Administration (SAMHSA), usually comprising a facility, staff, administration, patients, and services, that engages in supervised assessment and treatment, using methadone, buprenorphine, L-alpha acetyl methadol, or naltrexone, of individuals who are addicted to opioids. An OTP can exist in a number of settings including, but not limited to, intensive outpatient, residential, and hospital settings. Services may include medically supervised withdrawal and/or maintenance treatment, along with various levels of medical, psychiatric, psychosocial, and other types of supportive care.[15]

Opioid treatment services (OTS): An umbrella term that encompass es a variety of pharmacological and nonpharmacological treatment modalities. This term broadens understanding of opioid treatments to include all medications used to treat opioid use disorders and the psychosocial treatment that is offered concurrently with these pharmacotherapies. Pharmacological agents include opioid agonist medications such as methadone and buprenorphine, and opioid antagonist medications such as naltrexone.[4]

Opioid use disorder: A substance use disorder involving opioids. See "Substance Use Disorder."

Opioid withdrawal syndrome: Over time, morphine and its analogs induce tolerance and neuroadaptive changes that are responsible for rebound hyperexcitability when the drug is withdrawn. The withdrawal syndrome includes craving, anxiety, dysphoria, yawning, sweating, piloerection (gooseflesh), lacrimation (excessive tear formation), rhinorrhea (running nose), insomnia, nausea or vomiting, diarrhea, cramps, muscle aches, and fever. With short-acting drugs, such as morphine or heroin, withdrawal symptoms may appear within 8–12 hours of the last dose of the drug, reach a peak at 48–72 hours, and clear after 7–10 days. With longer-acting drugs, such as methadone, onset of withdrawal symptoms may not occur until 1–3 days after the last dose; symptoms peak between the third and eighth day and may persist for several weeks, but are generally milder than those that follow morphine or heroin withdrawal after equivalent doses.[18]

Overdose: The inadvertent or deliberate consumption of a dose much larger than that either habitually used by the individual or ordinarily used for treatment of an illness, and likely to result in a serious toxic reaction or death.[4]

Patient: As used in this document, an individual receiving alcohol, tobacco, and/or other drug or addictive disorder treatment. The terms "client" and "patient" sometimes are used interchangeably, although staff in nonmedical settings more commonly refer to "clients."[4]

Physical dependence: State of physical adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, and/or decreasing blood level of a substance and/or administration of an antagonist.[15]

Psychosocial treatment: Any nonpharmacological intervention carried out in a therapeutic context at an individual, family, or group level. Psychosocial interventions may include structured, professionally administered interventions (eg, cognitive behavior therapy or insight-oriented psychotherapy) or nonprofessional interventions (eg, self-help groups and nonpharmacological interventions from traditional healers).[12]

Precipitated withdrawal: A condition that occurs when an opioid agonist is displaced from the opioid receptors by an antagonist. It is also possible for a partial agonist to precipitate withdrawal.[18]

Recovery: A process of sustained action that addresses the biological, psychological, social, and spiritual disturbances inherent in addiction. This effort is in the direction of a consistent pursuit of abstinence, addressing impairment in behavioral control, dealing with cravings, recognizing problems in one's behaviors and interpersonal relationships, and dealing more effectively with emotional responses. Recovery actions lead to reversal of negative, self-defeating internal processes and behaviors, allowing healing of relationships with self and others. The concepts of humility, acceptance, and surrender are useful in this process. (Note: ASAM continues to explore, as an evolving process, improved ways to define Recovery.)[4]

Relapse: A process in which an individual who has established abstinence or sobriety experiences recurrence of signs and symptoms of active addiction, often including resumption of the pathological pursuit of reward and/or relief through the use of substances and other behaviors. When in relapse, there is often disengagement from recovery activities. Relapse can be triggered by exposure to rewarding substances and behaviors, by exposure to environmental cues to use, and by exposure to emotional stressors that trigger heightened activity in brain stress circuits. The event of using or acting out is the latter part of the process, which can be prevented by early intervention.[4]

Sedative, hypnotic, or anxiolytics: This class of substances includes all prescription sleeping medications and virtually all prescription antianxiety medications. Nonbenzodiazepine antianxiety medications, such as buspirone and gepirone, are not included in this class because they are not associated with significant misuse.[21]

Sobriety: A state of sustained abstinence with a clear commitment to and active seeking of balance in the biological, psychological, social, and spiritual aspects of an individual's health and wellness that were previously compromised by active addiction.[4]

Spontaneous withdrawal: A condition that occurs when an individual who is physically dependent on an opioid agonist suddenly discontinues or markedly decreases opioid use.[22]

Stabilization: Includes the medical and psychosocial processes of assisting the patient through acute intoxication and withdrawal to the attainment of a medically stable, fully supported, substance-free state. This often is done with the assistance of medications, though in some approaches to detoxification, no medication is used.[15]

Substance use disorder: Substance use disorder is marked by a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues to use alcohol, tobacco, and/or other drugs despite significant related problems. Diagnostic criteria are given in the DSM-5. Substance use disorder is the new nomenclature for what was included as substance dependence and substance abuse in the DSM-IV.[16]

Tolerance: A decrease in response to a drug dose that occurs with continued use. If an individual is tolerant to a drug, increased doses are required to achieve the effects originally produced by lower doses. Both physiological and psychosocial factors may contribute to the development of tolerance. Physiological factors include metabolic and functional tolerance. In metabolic tolerance, the body can eliminate the substance more readily, because the substance is metabolized at an increased rate. In functional tolerance, the central nervous system is less sensitive to the substance. An example of a psychosocial factor contributing to tolerance is behavioral tolerance, when learning or altered environmental constraints change the effect of the drug. Acute tolerance refers to rapid, temporary accommodation to the effect of a substance after a single dose. Reverse tolerance, also known as sensitization, refers to a condition in which the response to a substance increased with repeated use. Tolerance is one of the criteria of the dependence syndrome.[18]

Withdrawal management: Withdrawal management describes services to assist a patient's withdrawal. The liver detoxifies, but clinicians manage withdrawal.[10]

INTRODUCTION

Purpose

The American Society of Addiction Medicine (ASAM) developed the *National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use* (the "*Practice Guideline*") to provide information on evidence-based treatment of opioid use disorder. This guideline is intended to assist clinicians in the decision-making process for prescribing pharmacotherapies and psychosocial treatments to patients with opioid use disorder.

Specifically, the *Practice Guideline* helps in the following:

(1) Identifies current practices and outstanding questions regarding the safe and effective use of medications for the treatment of opioid use disorder.
(2) Uses a methodology that integrates evidence-based practices and expert clinical judgment to develop recommendations on best practices in opioid use disorder treatment.
(3) Presents best practices in a cohesive document for clinicians' use to improve the effectiveness of opioid use disorder treatment.

Background on Opioid Use Disorder

Opioid use disorder is a chronic, relapsing disease, which has significant economic, personal, and public health consequences. Many readers of this *Practice Guideline* may recognize the term "opioid use disorder" as it is used in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5) developed by the American Psychiatric Association; others may be more familiar with the term "opioid dependence," as used in previous editions of the DSM.

The ASAM defines addiction as "a primary, chronic disease of brain reward, motivation, memory, and related circuitry," with a "dysfunction in these circuits" being reflected in "an individual pathologically pursuing reward and/or relief of withdrawal symptoms by substance use and other behaviors." In this context, the preferred term by ASAM for this serious bio-psycho-social-spiritual illness would be "addiction involving opioid use." ASAM views addiction as a fundamental neurological disorder of "brain reward, motivation, memory, and related circuitry," and recognizes that there are unifying features in all cases of addiction, including substance-related addiction and nonsubstance-related addiction. It is clear that a variety of substances commonly associated with addiction work on specific receptors in the nervous system and on specific neurotransmitter systems. Specific pharmacological agents used in the treatment of addiction exert their effects via their actions on specific receptors. Hence, the medications used in the treatment of addiction have specific efficacy based on their own molecular structure and the particular neurotransmitters affected by that medication. Medications developed for the treatment of addiction involving opioid use may have benefits in the treatment of addiction involving an individual's use of other substances. For instance, naltrexone (US Food and Drug Administration [FDA]), for the treatment of opioid dependence using DSM, 4th Edition (DSM-IV) terminology, is also US FDA-approved for the treatment of alcohol dependence, as per the DSM-IV guidelines.

The ASAM recognizes that research is yet to be done to confirm the specificity of its conceptualization of addiction as a medical and a psychiatric illness (note: the International Classification of Diseases-10 [ICD-10], and the American Medical Association in various policy and position statements recognize addiction as both a medical and a psychiatric disorder). ASAM encourages clinicians, researchers, educators, and policy makers to use the term "addiction" regardless of whether the patient's condition at a given point in its natural history appears to more prominently involve opioid use or alcohol use, nicotine use, or engagement in addictive behaviors such as gambling. Given the widespread North American application of the DSM's categorization of disorders, this *Practice Guideline* will, for the sake of brevity and convention, use the term "opioid use disorder."

Epidemiology

According to the 2013 National Survey on Drug Use and Health (NSDUH),[5] 4.5 million individuals were current nonmedical users of prescription opioids (past month) and 1.9 million individuals met DSM-IV criteria for abuse or dependence of prescription opioids. In addition, the NSDUH reported that 289,000 people were current (past month) users of heroin

and 517,000 met DSM IV criteria for abuse or dependence in 2013. The rate of prescription opioid use for nonmedical purposes was 1.7% in persons 12 years and older. However, the rate of prescription opioid use among youth aged 12–17 declined from 3.2% in 2002 and 2003 to 1.7% in 2013. Importantly, nonmedical use of prescription opioids has been shown to be associated with the initiation of heroin use. In a study pooling data from the NSDUH from 2002 to 2012, the incidence of heroin use was 19 times greater among individuals who reported prior nonmedical use of prescription opioids compared to individuals who did not report prior nonmedical prescription opioid use.[23]

Mortality and Morbidity

Opioid use is associated with increased mortality. The leading causes of death in people using opioids for non-medical purposes are overdose and trauma.[6] The number of unintentional overdose deaths from prescription opioids has more than quadrupled since 1999.[24]

Opioid use increases the risk of exposure to HIV, viral hepatitis, and other infectious agents through contact with infected blood or body fluids (eg, semen) that results from sharing syringes and injection paraphernalia, or through unprotected sexual contact. Similarly, it increases the risk of contracting infectious diseases such as HIV/AIDS and hepatitis because people under the influence of drugs may engage in risky behaviors that can expose them to these diseases.[6]

Importantly, injection drug use (IDU) is the highest-risk behavior for acquiring hepatitis C virus (HCV) infection and continues to drive this epidemic. Of the 17,000 new HCV infections in the United States in 2010, more than half (53%) involved IDU. In 2010, hepatitis B virus (HBV) infection rates were estimated to be 20% higher among people who engaged in IDU in the United States.[25]

Scope of Guideline

This *Practice Guideline* was developed to assist in the evaluation and treatment of opioid use disorder. Although there are existing guidelines for the treatment of opioid use disorder, none have included all of the medications used for its treatment at present. Moreover, few of the existing guidelines address the needs of special populations such as pregnant women, individuals with co-occurring psychiatric disorders, individuals with pain, adolescents, or individuals involved in the criminal justice system.

Overall, the *Practice Guideline* contains recommendations for the evaluation and treatment of opioid use disorder, opioid withdrawal management, psychosocial treatment, special populations, and opioid overdose.

(1) *Part 1:* Contains guidelines on the evaluation of opioid use disorder
(2) *Part 2:* Provides recommendations regarding treatment options
(3) *Part 3:* Describes the treatment of opioid withdrawal
(4) *Parts 4–6:* Provide guidelines on medications for treating opioid use disorder
(5) *Part 7:* Describes psychosocial treatment used in conjunction with medications

(6) *Parts 8–12:* Provide guidelines for treating special populations and circumstances
(7) *Part 13:* Describes the use of naloxone in treating opioid overdose

Included and Excluded Medications

The medications covered in this guideline include the following:

(1) Methadone (part 4)
(2) Buprenorphine (part 5)
(3) Naltrexone in oral and extended-release injectable formulations (part 6)
(4) Naloxone (part 13)

All of these medications act directly upon the opioid receptors, particularly the mu-subtype. Methadone is a mu-receptor agonist; buprenorphine is a partial mu-receptor agonist; and naltrexone is an antagonist. Naloxone is a fast-acting antagonist used to reverse opioid overdose, a condition that may be life-threatening. Because of the differing actions of these medications at the receptor level, they can have very different clinical effects during treatment.

Other medications show promise for the treatment of opioid use disorder; however, there is insufficient evidence at this writing to make a full analysis of their effectiveness. For example, whereas not US FDA-approved for opioid withdrawal syndrome in the United States, it is recognized that clonidine, an alpha-2 adrenergic agonist, has been in use in clinical settings for 25 years. Lofexidine (known as BritLofex, Britannia Pharmaceuticals) is approved for treating opioid withdrawal use in the United Kingdom. Because of their long history of off-label use in the United States, clonidine and buprenorphine are described for opioid withdrawal syndrome in this *Practice Guideline*. Again, there are other off-label medications for withdrawal management in the treatment of opioid use disorder (eg, tramadol) that have been excluded from this guideline because there is insufficient evidence to make a full analysis of their effectiveness or consensus recommendations for their use at this time.

The ASAM recognizes that withdrawal management and withdrawal management medications could be potential topics for future guideline development. ASAM will regularly review its published guidelines to determine when partial or full updates are needed. The emergence of newly approved medications and new research will be considered as part of this process. It is also recognized that ASAM may develop guidelines or consensus documents on topics addressed in this *Practice Guideline* (eg, urine drug testing). If that occurs before any update to this *Practice Guideline*, it is to be assumed that the recommendations in the latter documents will take precedence until this *Practice Guideline* is updated.

Intended Audience

This *Practice Guideline* is intended for all clinicians, at any level, involved in evaluating for, and/or providing, opioid use disorder treatment in the United States. The intended audience falls into the following broad groups:

(1) Physicians involved in the assessment, diagnosis, and treatment of opioid use disorder. General practice physicians (including family practitioners, pediatricians, obstetricians, and gynecologists) are often first-line providers of medical care related to opioid use disorder and are a key audience for the guideline.

(2) Clinicians involved with the completion of health assessments and delivery of health services to special populations.

(3) Clinicians involved in making an initial assessment and offering psychosocial treatments in conjunction with medications to treat opioid use disorder.

(4) Clinical case managers responsible for clinical care support, coordination of health-related and social services, and tracking of patient adherence to the treatment plan.

Qualifying Statement

The ASAM *Practice Guideline* is intended to aid clinicians in their clinical decision-making and patient management. It strives to identify and define clinical decision-making junctures that meet the needs of *most patients* in *most circumstances*. The ultimate judgment about care of a particular patient must be made together by the clinician and the patient in light of all the circumstances presented by the patient. As a result, situations may arise in which deviations from the *Practice Guideline* may be appropriate. Clinical decision-making should involve consideration of the quality and availability of expertise and services in the community wherein care is provided.

In circumstances in which the *Practice Guideline* is being used as the basis for regulatory or payer decisions, improvement in quality of care should be the goal. Finally, prescribed courses of treatment contained in recommendations in this *Practice Guideline* are effective only if the recommendations, as outlined, are followed. Because lack of patient understanding and adherence may adversely affect outcomes, clinicians should make every effort to engage the patient's understanding of, and adherence to, prescribed and recommended pharmacological and psychosocial treatments. Patients should be informed of the risks, benefits, and alternatives to a particular treatment and should be shared parties to decision-making whenever feasible. Recommendations in this *Practice Guideline* do not supersede any federal or state regulation.

METHODOLOGY

Overview of Approach

These guidelines were developed using the RAND/UCLA Appropriateness Method (RAM) – a process that combines scientific evidence and clinical knowledge to determine the appropriateness of a set of clinical procedures.[26] This process is particularly appropriate for these guidelines for two reasons. First, there are very few randomized clinical trials directly comparing the approved medications for the treatment of opioid use disorder. Second, evidence supporting the efficacy of the individual medications reflects varying years of research and varying levels of evidence (eg, nonrandomized studies, retrospective studies). The randomized clinical trial (RCT) is the gold standard for evidence-based medicine. When data are lacking from RCT, other methods must be used to help clinicians make the best choices. In addition, these guidelines are unique in that they include all three of the medications approved at present by the US FDA in multiple formulations, and they address the needs of special populations such as pregnant women, individuals with pain, adolescents, individuals with co-occurring psychiatric disorder, and individuals in criminal justice. Such special populations are often excluded from RCTs, making the use of RCT data even more difficult. The RAM process combines the best available scientific evidence combined with the collective judgment of experts to yield statements about the appropriateness of specific procedures that clinicians can apply to their everyday practice.

The ASAM's Quality Improvement Council (QIC) was the oversight committee for the guideline development. The QIC appointed a Guideline Committee to participate throughout the development process, rate treatment scenarios, and assist in writing. In selecting the committee members, the QIC made every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of relationships with industry and other entities among members of the Guideline Committee. All QIC members, committee members, and external reviewers of the guideline were required to disclose all current related relationships, which are presented in Appendices III, IV, and V.

The Guideline Committee was comprised of 10 experts and researchers from multiple disciplines, medical specialties, and subspecialties, including academic research, internal medicine, family medicine, addiction medicine, addiction psychiatry, general psychiatry, obstetrics/gynecology, and clinical neurobiology. Physicians with both allopathic and osteopathic training were represented in the Guideline Committee. The Guideline Committee was assisted by a technical team of researchers from the Treatment Research Institute (TRI) affiliated with the University of Pennsylvania (see page 2), and worked under the guidance of Dr. Kyle Kampman who led the TRI team as Principal Investigator in implementing the RAM.

The RAM process is a deliberate approach encompassing review of existing guidelines, literature reviews, appropriateness ratings, necessity reviews, and document development. The steps are summarized in the flow chart in "Exhibit 1 Methodology."

Task 1: Review of Existing Guidelines

Review of Existing Clinical Guidelines

All existing clinical guidelines that addressed the use of medications and psychosocial treatments in the treatment of opioid use disorders including special populations (eg pregnant women, individuals with pain, and adolescents), and that were published during the period from January 2000 to April 2014, were identified and reviewed. In total, 49 guidelines were identified and 34 were ultimately included in the analysis. See "Appendix I" for a list of the guidelines that were reviewed. The included guidelines offered evidence-based recommendations for the treatment of opioid use disorder using methadone, buprenorphine, naltrexone, and/or naloxone.

The majority of existing clinical guidelines are based on systematic reviews of the literature including appropriateness

criteria used in the RAM. Therefore, the aim of this exercise was not to re-review all of the research literature, but to identify within the existing clinical guidelines how they addressed common questions or considerations that clinicians are likely to raise in the course of deciding whether and how to use medications as part of the treatment of individuals with opioid use disorder.

Analysis of Clinical Guidelines

On the basis of the previously reviewed existing clinical guidelines, an analytic table was created and populated to display the identified key components. This table served as the foundation for development of hypothetical statements. The hypothetical statements were sentences describing recommendations derived from the analysis of the clinical guidelines.

Preparation of Literature Review on Psychosocial Interventions

A review of the literature on the efficacy of psychosocial treatment delivered in conjunction with medications for the treatment of opioid use disorder was conducted. This review was partially supported by funding from the National Institute on Drug Abuse (NIDA). Articles were identified for inclusion in the review through searches conducted in two bibliographic databases (eg, PsycINFO and PubMed) using predefined search terms and established selection criteria. Titles and abstracts were reviewed for inclusion by two members of the research team.

To increase the overall relevance of the review, the search was limited to articles in the 6-year period from 2008 to the present. In the event that the article reflected a secondary analysis of data from a relevant study, the original study was included in the literature review. In addition, findings from three prominent systematic reviews (ie, 2007 review on psychosocial interventions in pharmacotherapy of opioid dependence prepared for the Technical Development Group for the World Health Organization, "Guidelines for Psychosocially Assisted Pharmacotherapy of Opioid Dependence," and two 2011 Cochrane reviews examining psychosocial and pharmacological treatments for opioid withdrawal management and psychosocial interventions combined with agonist treatment) were summarized.[27–29]

The literature search yielded 938 articles. The titles and abstracts were reviewed to determine if the study met the inclusion/exclusion criteria, and those that did not ($n = 787$) were removed. The remaining 151 articles were then reviewed for inclusion, and 27 articles were ultimately retained for use in the literature review as the others did not meet the predetermined inclusion/exclusion criteria. These articles, along with the relevant systematic reviews of the literature, are described in the literature review in the next section.

Task 2: Identification of Hypothetical Statements and Appropriateness Rating

RAND/UCLA Appropriateness Method

The first step in the RAM is to develop a set of hypothetical statements, which were derived from the guideline analysis and literature review described in the previous section, for appropriateness rating.

The analysis and literature review generated a list of 245 hypothetical statements that reflected recommended medical or psychosocial treatment. Each member of the Guideline Committee reviewed the guideline analysis and literature review, and privately rated 245 hypothetical clinical statements on a nine-point scale of "appropriateness." In the context of this *Practice Guideline*, the meaning of appropriateness was defined as:

> *"A statement, procedure or treatment is considered to be appropriate if the expected health benefit (eg, increased life expectancy, relief of pain, reduction in anxiety, improved functional capacity) exceeds the expected negative consequences (eg, mortality, morbidity, anxiety, pain) by a sufficiently wide margin that the procedure is worth doing, exclusive of cost."*

An appropriateness score of 1 meant that the statement was "highly inappropriate." An appropriateness rating of 9 meant that the statement was "highly appropriate." These appropriateness statements were meant to identify a lack of consensus in existing guidelines and research literature.

Guideline Committee Meeting

Upon completion and collection of the individual Guideline Committee member ratings, 201 out of the 245 hypothetical statements were identified as meeting the criteria for consensus. The remaining 44 statements had divergent ratings. On September 15, 2014, the Guideline Committee met in Washington, District of Columbia, to discuss the hypothetical clinical statements. At this meeting, the committee came to consensus on the hypothetical statements. After the meeting, the information gathered was used to revise several of the statements; and the Guideline Committee was asked to re-rate the revised statements.

Literature Review

A supplementary literature review was also conducted to identify relevant studies that might resolve statements that had resulted in divergent ratings during the Guideline Committee meeting. Information relating to the vast majority of these divergent ratings was subsequently found within the existing guideline data set, and consequently included in the first draft of the *Practice Guideline*.

For the topics and questions for which answers were not found in the existing guideline data set, a full literature review was conducted. The topics and questions for which no further clarification was found in the literature were considered "gaps" that require additional research before inclusion in this guideline. These gaps in the literature were: urine drug testing; patients using marijuana; the safety of delivering injectable naltrexone doses to patients with high metabolism every 3 weeks; and the safety of adding full agonists to treatment with buprenorphine for pain management.

Creation and Revision of Guideline Outline

All the identified appropriate/uncertain hypothetical statements and supporting research were incorporated into an outline defining each specific section to be included in

the final *Practice Guideline*. The draft outline, review of existing guidelines, and literature review were all sent to the Guideline Committee members for review and discussion during two web teleconferences and through private communication. Two teleconferences were held to ensure full participation from members of the Guideline Committee.

Task 3: Comparative Analysis, Review, and Necessity Rating

Committee Review and Rating

The Guideline Committee then re-rated the 211 "appropriate" hypothetical statements for necessity. When rating for necessity, the Guideline Committee members were asked to adhere to the following guidance:

A statement was considered *necessary* when all the following criteria were met:

(1) It would be considered improper care not to provide this service.
(2) Reasonable chance exists that this procedure and/or service will benefit the patient. (A procedure could be *appropriate* if it had a low likelihood of benefit, but few risks; however, such procedures would not be *necessary*.)
(3) The benefit to the patient is of significance and certainty. (A procedure could be *appropriate* if it had a minor but almost certain benefit, but it would not be *necessary*.)

Necessity is a more stringent criterion than appropriateness. If a procedure is necessary, this means that the expected benefits outweigh the expected harms (ie, it is appropriate), and that they do so by such a margin that the physician must recommend the service. Of course, patients may decline to follow their physician's recommendations.[26]

Of the 211 rated statements, 184 hypothetical statements met the criteria for being both appropriate and necessary, and were incorporated in the guideline.

Final Draft Outline

The final draft outline highlighted hypothetical statements that had been determined to rise to the level of necessity.

Task 4: Drafting the National Practice Guideline

Draft and Review

A first draft of the *Practice Guideline* was created using the Guideline Committee's recommendations resulting from supporting evidence and the appropriateness and necessity ratings discussed above. The first draft of the *Practice Guideline* was sent to the Guideline Committee for review and electronic comment. During a subsequent teleconference in January 2015, the Guideline Committee discussed the comments received via first review. Revisions were made to the draft, which went again through subsequent reviews by the Guideline Committee and the ASAM Quality Council throughout February and March 2015.

Task 5: External Review

External Review

The ASAM sought input from ASAM members – patient and caregiver groups, stakeholders including experts from the criminal justice system, government agencies, other professional societies, and hospitals and health systems. ASAM also made the document and a qualitative review guide available to ASAM members and the general public for a one week period of review and comment. The final draft *Practice Guideline* was submitted to the ASAM Board of Directors in April 2015.

Exhibit 1: Methodology

Review of existing guidelines
49 existing guidelines were identified; 34 guidelines were included in the RAM process.

Literature review on psychosocial treatment

Development of hypothetical statements
Using the existing clinical guidelines and literature from the psychosocial literature review, 245 hypothetical statements were created and sent to the Guideline Committee to rate for their appropriateness.

Initial appropriateness rating
The Guideline Committee reviewed the 245 hypothetical statements for appropriateness. Out of the 245 statements, 201 reached consensus for appropriateness and 44 had divergent ratings.

Guideline committee meeting
The Guideline Committee met to discuss the appropriateness of the remaining 44 divergent hypothetical statements and then was asked to re-rate the statements for their appropriateness.

Secondary appropriateness rating
The Guideline Committee reviewed the 44 hypothetical statements for appropriateness. Out of these 44, 10 were deemed appropriate. A total of 211 hypothetical statements were deemed appropriate to include in the guideline.

Necessity rating
The Guideline Committee reviewed the 211 hypothetical statements for necessity. Of the 211, a total of 184 hypothetical statements were deemed both appropriate and necessary to include in the guideline.

PART 1: ASSESSMENT AND DIAGNOSIS OF OPIOID USE DISORDER

Comprehensive Assessment

The ASAM *Standards of Care for the Addiction Specialist Physician* (the "ASAM Standards") describe the importance of comprehensive assessment. Though the assessment process is ongoing for the patient with substance use disorder, a comprehensive assessment is "a critical aspect of

patient engagement and treatment planning'' and should be conducted during the initial phase of treatment.[10] The assessment is not necessarily the first visit; it is critical, however, to determine emergent or urgent medical problems. Patients with opioid use disorder often have other physiological or psychiatric conditions that may complicate their treatment. These concomitant medical and psychiatric conditions may need immediate attention and require transfer to a higher level of care (see ''Part 11: Special Populations: Individuals With Co-occurring Psychiatric Disorders'').

Medical History

The patient's medical history should include screening for concomitant medical conditions and routine identification of medications, allergies, pregnancy, family medical history, and so on. Particular attention should be paid to the following: history of infectious diseases such as hepatitis, HIV, and TB; acute trauma; psychiatric, substance use, addictive behavior, and addiction treatment history; and any previous history of pharmacotherapy. An intake of the patient's social history and assessment of readiness for change including identification of any facilitators and barriers are also components of the medical history.

Physical Examination

As part of the comprehensive assessment of patients with opioid use disorder, a physical examination should be completed by the prescriber him/herself (the clinician authorizing the use of a medication for the treatment of opioid use disorder), another member of the clinician's health system, or the prescribing physician. Further, the responsible clinician should assure that a current physical examination (in accordance with the ASAM Standards) is contained within the patient medical record before a patient is started on a new medication for the treatment of his/her opioid use disorder.

The examination should include identifying objective physical signs of opioid intoxication or withdrawal. See Table 1 for a list of common signs of intoxication or withdrawal. In addition, the examination should evaluate objective signs of substance use disorders. See Table 2 for a list of physical signs of substance use disorders (including opioid use disorder).

Special attention should be given to identifying IDU by the presence of new or older puncture marks. Common injection sites are inside the elbow (cubital fossa) and forearm, but other sites on the extremities may be injection sites.

TABLE 1. Common Signs of Opioid Intoxication and Withdrawal

Intoxication Signs	Withdrawal Signs
Drooping eyelids	Restlessness, irritability, anxiety
Constricted pupils	Insomnia
Reduced respiratory rate	Yawning
Scratching (due to histamine release)	Abdominal cramps, diarrhea, vomiting
Head nodding	Dilated pupils
	Sweating
	Piloerection

TABLE 2. Objective Physical Signs in Substance Use Disorders

System	Findings
Dermatologic	Abscesses, rashes, cellulitis, thrombosed veins, jaundice, scars, track marks, pock marks from skin popping
Ear, nose, throat, and eyes	Pupils pinpoint or dilated, yellow sclera, conjunctivitis, ruptured eardrums, otitis media, discharge from ears, rhinorrhea, rhinitis, excoriation or perforation of nasal septum, epistaxis, sinusitis, hoarseness, or laryngitis
Mouth	Poor dentition, gum disease, abscesses
Cardiovascular	Murmurs, arrhythmias
Respiratory	Asthma, dyspnea, rales, chronic cough, hematemesis
Musculoskeletal and extremities	Pitting edema, broken bones, traumatic amputations, burns on fingers
Gastrointestinal	Hepatomegaly, hernias

Assessment and History Considerations Specific to Females

Use of contraception and determination of pregnancy are factors in choosing treatment options for women with opioid use disorder. Contraception and reproductive health are topics of discussion within the assessment process of female patients who are considering opioid use disorder treatment. Clinicians and female patients should keep in mind that fertility increases as treatment becomes effective. Case management plans may need to include referral to gynecological services for female patients. An in-depth discussion of the treatment of opioid use disorder in pregnant women is described later in ''Part 8: Special Populations: Pregnant Women.''

Laboratory Tests

Initial lab testing should include hepatitis C and HIV testing. Hepatitis serology and vaccination are recommended. Hepatitis A and B testing and vaccination should be offered when appropriate. As above, women of childbearing potential and age should be tested for pregnancy. Tuberculosis testing and testing for sexually transmitted infections, including syphilis, may be considered.

A complete blood count and liver function study should be conducted to screen for liver dysfunction, infection, and other medical conditions. Abnormal results may require further investigation.

Assessment for Mental Health Status and Psychiatric Disorder

Patients being evaluated for opioid use disorder, and/or for possible medication use in the treatment of opioid use disorder, should undergo an evaluation of possible co-occurring psychiatric disorders. During the assessment process and physical examination, it is important for the clinician to assess for mental health status consistent with the ASAM Standards.

In the ASAM Standards, I.1 indicates that the physician ''assures that an initial comprehensive, multicomponent assessment is performed for each patient, either by performing it her/himself or by assuring it is conducted in full or in part by another qualified professional within the system in which she/he is working.'' A thorough medical and psychiatric history and family history is indicated as a component of this same standard. Patients

who are determined as exhibiting urgent or emergent psychiatric conditions, or who are psychiatrically unstable and represent a danger to themselves or others, should be referred to the appropriate level of care for their safety and the safety of others. Further specialty evaluation may be warranted depending on severity of indicators for psychiatric instability. Indicators of psychiatric instability or disorder include acute suicidal or homicidal ideation, acute psychosis, and delirium.

Assessment for Alcohol and Substance Use and Treatment History

A careful evaluation of current and past use of alcohol and drugs, including nonmedical use of prescription medications, is required to diagnose opioid use disorder. Because opioid use disorder may co-occur with other use disorders, the evaluator should assess frequency and quantity of use.

Completing a history of opioid drug use with a patient who has been identified as using opioids should focus on the following:

(1) type and amount of opioid(s) used recently;
(2) route of administration;
(3) last use;
(4) treatment history; and
(5) problems resulting from drug use.

The amount of drug being consumed will impact the likelihood and severity of withdrawal symptoms when the drug is stopped, so it is useful to obtain an estimate of the amount used (each time and number of times per day).

Prescription Drug Monitoring Programs (PDMPs) offer information about prescription opioid use. They can serve as important resources for clinicians' use in completing full patient clinical assessments of opiate and other controlled substance use history, and it is recommended that they be utilized. It is recognized, as detailed in "Exhibit 2 Prescription Drug Monitoring Programs," that there is variation across states in terms of the level of operation of these programs, the extent of their data sharing across states, and state requirements for their use before prescribing controlled substances.

In addition, a history of outpatient and inpatient treatment for alcohol and other substance use disorders should be collected. Clinicians should ask for information about the type and duration of treatment and outcomes.

Assessment for Co-occurring Alcohol and Substance Use

Opioid use disorder often co-occurs with alcohol and other substance use disorders. Therefore, evaluation of co-occurring alcohol and substance use is recommended.

Clinicians should assess signs and symptoms of alcohol or sedative, hypnotic, or anxiolytic intoxication or withdrawal. Alcohol or sedative, hypnotic, or anxiolytic withdrawal may result in seizures, hallucinosis, or delirium, and may represent a medical emergency. Likewise, concomitant use of alcohol and sedatives, hypnotics, or anxiolytics with opioids may contribute to respiratory depression. Patients with significant co-occurring substance use disorders, especially severe alcohol or sedative, hypnotic, or anxiolytic use, may require a higher level of care.

An evaluation of past and current substance use should be conducted, and a determination as to whether addiction involving other substances or other behaviors is present. For instance, the regular use of marijuana or cannabinoids, tobacco or electronic nicotine delivery devices, or other drugs should not be a reason to suspend medication use in the treatment of addiction involving opioid use. Concurrent use of other drugs or active engagement in other addictive behaviors should lead to consideration of other treatment plan components for the patient. The presence of co-occurring substance use disorders should provoke a re-evaluation of the level of care that is in place for psychosocial treatment, along with pharmacological therapy. In most cases, co-occurring drug use will not represent a medical emergency. In such cases, patients can be treated for both their opioid use disorder and co-occurring alcohol or substance use disorders. However, ongoing use of other drugs may lead to poorer treatment outcomes. Evidence does demonstrate that individuals who are actively using other substances during opioid use disorder treatment have a poorer prognosis.[30-32]

The Guideline Committee cautioned against excluding patients from treatment for their opioid use disorder because they are using marijuana or other psychoactive substances that do not interact with opioids, and that are not prescribed by their physician. Whereas there is a paucity of research examining this topic, evidence demonstrates that patients under treatment have better outcomes than those not retained under treatment.[33,34] Suspension of opioid use disorder treatment may increase the risk for death from overdose, accidents, or other health problems. However, continued use of marijuana or other psychoactive substances may impede treatment for opioid use disorder; thus, an approach emphasizing cessation of all unprescribed substances is likely to result in the best results. Further research is needed on the outcomes of patients in opioid use disorder treatment who are continuing the nonmedical use of psychoactive substances.

Assessment for Tobacco Use

Tobacco use should be queried, and the benefits of cessation should be promoted routinely with patients presenting for evaluation and treatment of opioid use disorder. Several studies have demonstrated that smoking cessation improves long-term outcomes among individuals receiving treatment for substance use disorders.[35-37]

Assessment of Social and Environmental Factors

Clinicians should conduct an assessment of social and environmental factors (as outlined in the ASAM Standards) to identify facilitators and barriers to addiction treatment and specifically to pharmacotherapy. Before a decision is made to initiate a course of pharmacotherapy for the patient with opioid use disorder, the patient should receive a multidimensional assessment in fidelity with *The ASAM Criteria: Treatment Criteria for Addictive, Substance-Related, and Co-occuring Conditions* (the "ASAM Criteria"). The ASAM Patient Placement Criteria uses six dimensions to create a holistic biopsychosocial assessment of an individual to be used for service

Prescription drug monitoring programs
updated 1-26-14

Light Blue   **-- States with PDMP's**
Dark Blue — States with PDMP legislation, but program not fully operational
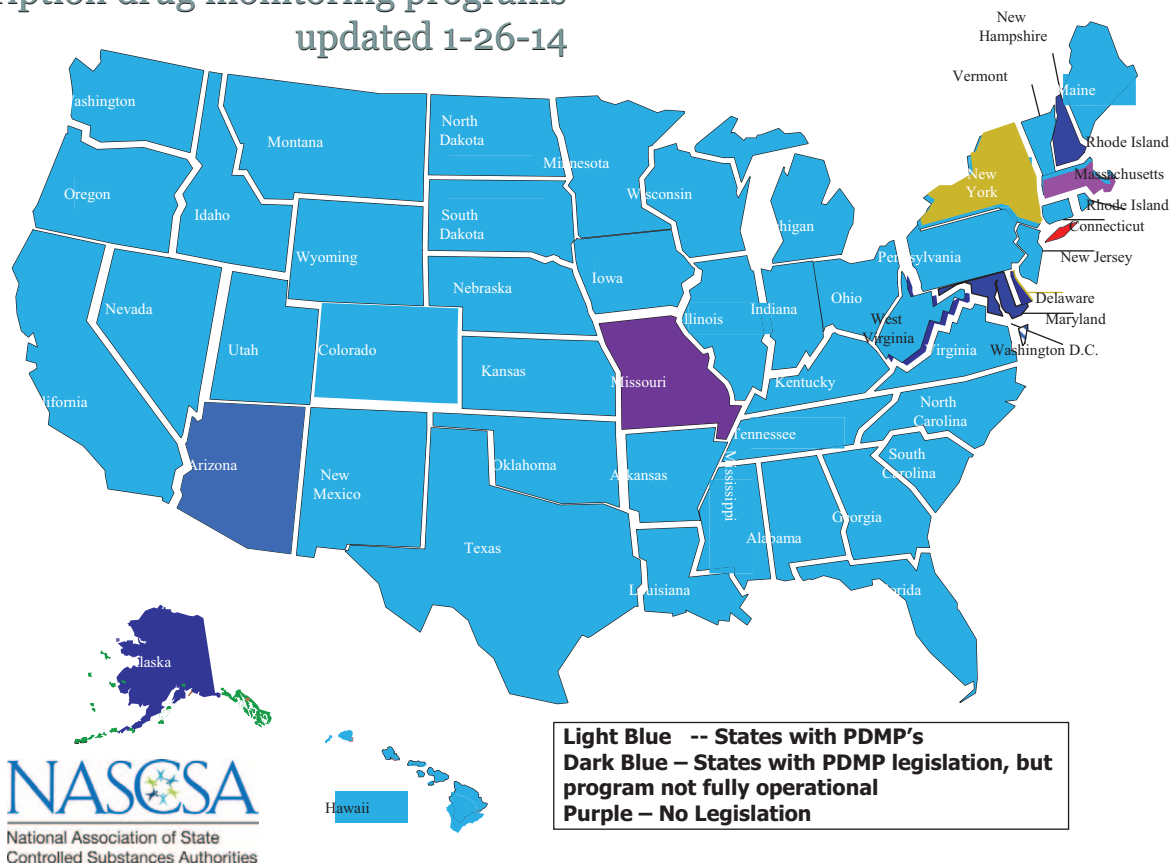**Purple — No Legislation**

Exhibit 2: Prescription Drug Monitoring Programs

planning and treatment. Dimension one is acute intoxication or withdrawal potential. Dimension two is biomedical conditions and conditions. Dimension three is emotional, behavioral, or cognitive conditions or complications. Dimension four is readiness for change. Dimension five is continued use or continued problem potential. Dimension six is recovery/living environment.[4] The use of medications for the patient with addiction involving opioid use can be appropriate across all levels of care. Pharmacotherapy is not a "level of care" in addiction treatment, but one component of multidisciplinary treatment. Whereas medication as a standalone intervention has been utilized in North America and internationally, ASAM recommends that the use of medications in the treatment of addiction be part of a broad bio-psycho-social-spiritual intervention appropriate to the patient's needs and to the resources available in the patient's community. Addiction should be considered a bio-psycho-social-spiritual illness, for which the use of medication(s) is but only one component of overall treatment.

Diagnosing Opioid Use Disorder

Opioid use disorder is primarily diagnosed on the basis of the history provided by the patient and a comprehensive assessment that includes a physical examination. Corroborating information reported by significant others can be used to confirm the diagnosis, especially when there is lack of clarity or inconsistency in information. Other clinicians may make a diagnosis of opioid use disorder; however, provider confirmation of the diagnosis is required before medications are prescribed. This is discussed further in later parts that address specific medications.

DSM-5 Criteria for Diagnosis

The diagnosis of opioid use disorder is based on criteria outlined in the DSM-5. The criteria describe a problematic pattern of opioid use leading to clinically significant impairment or distress. There are a total of 11 symptoms and severity is specified as either mild (presence of 2-3 symptoms), moderate (presence of 4-5 symptoms) or severe (presence of 6 or more symptoms) within a 12 month period. Opioid use disorder requires that at least two of the following 11 criteria be met within a twelve-month period: (1) taking opioids in larger amounts or over a longer period of time than intended; (2) having a persistent desire or unsuccessful attempts to reduce or control opioid use; (3) spending excess time obtaining, using or recovering from opioids; (4) craving for opioids; (5) continuing opioid use causing inability to fulfill work, home, or school responsibilities; (6) continuing opioid use despite having persistent social or interpersonal problems; (7) lack of involvement in social, occupational or recreational activities; (8) using opioids in physically hazardous situations; (9) continuing opioid use in spite of awareness of persistent physical or psychological problems; (10) tolerance, including need for increased amounts of opioids or diminished effect with continued use at the same

amount – as long as the patient is not taking opioids under medical supervision; and (11) withdrawal manifested by characteristic opioid withdrawal syndrome or taking opioids to relieve or avoid withdrawal symptoms – as long as the patient is not taking opioids under medical supervision.

More detail about diagnosing opioid use disorder is available in the American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.

Withdrawal Scales

There are a number of useful opioid withdrawal scales that can assist the clinician in evaluating patients with opioid use disorder by identifying and quantitating the severity of opioid withdrawal symptoms. The Objective Opioid Withdrawal Scale (OOWS), which relies on clinical observation, is useful in measuring and documenting the objectively measurable symptoms of opioid withdrawal. The Subjective Opioid Withdrawal Scale (SOWS) records the patient's rating of opioid withdrawal on a 16-item scale.[38] Finally, the Clinical Opioid Withdrawal Scale (COWS) includes 11 items, and contains signs and symptoms of opioid withdrawal, which are both objective and subjective in nature.[38]

Urine Drug Testing

Urine drug testing, or other reliable biological tests for the presence of drugs, during the initial evaluation and frequently throughout treatment, is highly recommended. There are a variety of toxicology tests available, some with greater and lesser reliability and validity. The person who is interpreting these labs should be very familiar with the methodology and the reliability. There is little research on the optimal frequency of testing. The recommendations given below are based on the consensus opinion of the Guideline Committee. The frequency of drug testing will be determined by a number of factors, including the stability of the patient, the type of treatment, the treatment setting, and the half-life of drugs in the matrix being tested. Patients will likely require more testing early in treatment or during periods of relapse. Patients participating in office-based treatment with buprenorphine may be tested at each office visit. Patients participating in treatment for opioid use disorder at Opioid Treatment Programs (OTPs) are mandated by the Federal law[39] to receive a minimum of eight drug tests per year, but may be tested more frequently based on clinical need. More detailed information on drug testing is contained in "*Drug Testing – A White Paper of the American Society of Addiction Medicine.*"[40]

Opioids are detectable in the urine for 1–3 days after use. A negative urine test combined with no history of withdrawal may indicate a lack of physical dependence. However, a negative urine test does not rule out opioid use, disorder, or physical dependence. Urine testing is also helpful to identify use of other psychoactive substances.

Summary of Recommendations

Assessment Recommendations

(1) First clinical priority should be given to identifying and making appropriate referral for any urgent or emergent medical or psychiatric problem(s), including drug-related impairment or overdose.

(2) Completion of the patient's medical history should include screening for concomitant medical conditions including infectious diseases (hepatitis, HIV, and TB), acute trauma, and pregnancy.

(3) A physical examination should be completed as a component of the comprehensive assessment process. The prescriber (the clinician authorizing the use of a medication for the treatment of opioid use disorder) may conduct this physical examination him/herself, or, in accordance with the ASAM Standards, ensure that a current physical examination is contained within the patient medical record before a patient is started on a new medication for the treatment of his/her addiction.

(4) Initial laboratory testing should include a complete blood count, liver function tests, and tests for hepatitis C and HIV. Testing for TB and sexually transmitted infections should also be considered. Hepatitis B vaccination should be offered, if appropriate.

(5) The assessment of women presents special considerations regarding their reproductive health. Women of childbearing age should be tested for pregnancy, and all women of childbearing potential and age should be queried regarding methods of contraception, given the increase in fertility that results from effective opioid use disorder treatment.

(6) Patients being evaluated for addiction involving opioid use, and/or for possible medication use in the treatment of opioid use disorder, should undergo (or have completed) an assessment of mental health status and possible psychiatric disorders (as outlined in the ASAM Standards).

(7) Opioid use is often co-occurring with other substance-related disorders. An evaluation of past and current substance use and a determination of the totality of substances that surround the addiction should be conducted.

(8) The use of marijuana, stimulants, or other addictive drugs should not be a reason to suspend opioid use disorder treatment. However, evidence demonstrates that patients who are actively using substances during opioid use disorder treatment have a poorer prognosis. The use of benzodiazepines and other sedative hypnotics may be a reason to suspend agonist treatment because of safety concerns related to respiratory depression.

(9) A tobacco use query and counseling on cessation of tobacco products and electronic nicotine delivery devices should be completed routinely for all patients, including those who present for evaluation and treatment of opioid use disorder.

(10) An assessment of social and environmental factors should be conducted (as outlined in the ASAM Standards to identify facilitators and barriers to addiction treatment, and specifically to pharmacotherapy). Before a decision is made to initiate a course of pharmacotherapy for the patient with opioid use disorder, the patient should receive a multidimensional assessment in fidelity with the ASAM Criteria. Addiction should be considered a bio-psycho-social-spiritual illness, for which the use of medication(s) is but only one component of overall treatment.

Diagnosis Recommendations

(1) Other clinicians may diagnose opioid use disorder, but confirmation of the diagnosis by the provider with prescribing authority and who recommends medication use must be obtained before pharmacotherapy for opioid use disorder commences.

(2) Opioid use disorder is primarily diagnosed on the basis of the history provided by the patient and a comprehensive assessment that includes a physical examination.

(3) Validated clinical scales that measure withdrawal symptoms, for example, the OOWS, SOWS, and the COWS, may be used to assist in the evaluation of patients with opioid use disorder.

(4) Urine drug testing during the comprehensive assessment process, and frequently during treatment, is recommended. The frequency of drug testing is determined by a number of factors, including the stability of the patient, the type of treatment, and the treatment setting.

Areas for Further Research

(1) More research is needed on best practices for drug testing during the initial evaluation and throughout the entire treatment process.

(2) Further research is needed on evidence-based approaches for treating opioid use disorder in patients who continue to use marijuana and/or other psychoactive substances.

(3) Whereas research indicates that offering tobacco cessation is a standard for all medical care, more research is needed before specific evidence-based recommendations can be made.

PART 2: TREATMENT OPTIONS

Introduction

Once the diagnosis of opioid use disorder has been established, and it has been determined that the patient is medically and psychiatrically stable, the next task is to decide on a course of treatment. Potential treatments include withdrawal management in conjunction with psychosocial treatment, or psychosocial treatment combined with one of three medications: methadone, buprenorphine, or naltrexone (oral or extended-release injectable formulations). Withdrawal management alone can be the first step, but is not a primary treatment for opioid use disorder and should ''only'' be considered as a part of a comprehensive and longitudinal plan of care that includes psychosocial treatment, with or without medication-assisted therapy.

The choice among available treatment options should be a shared decision between the clinician and the patient. There are a number of factors to consider in deciding what treatment to choose. Among the first considerations are the priorities of the patient, for instance: *Is the patient open to pharmacotherapy? What type of treatment setting does the patient prefer? Does the patient understand the physical dependence aspects of treatment medication?* A patient's past experiences with treatment for opioid use disorder should be considered as well. Of course, above all, evidence supporting the potential efficacy and safety of the various treatments is critically important.

For most patients with opioid use disorder, the use of medications (combined with psychosocial treatment) is superior to withdrawal management (combined with psychosocial treatment), followed finally by psychosocial treatment on its own. This is true for both agonist and partial agonist, and antagonist medications. Evidence suggests that methadone maintenance treatment is superior to withdrawal management alone and significantly reduces opioid drug use.[41] Further, mortality is lower in patients on methadone, as compared to those not undergoing treatment.[6] Methadone also lowers the risk of acquiring or spreading HIV infection.[42,43] In clinical studies, evidence favors buprenorphine, compared to no treatment, in decreasing heroin use and improving treatment retention.[33,44] Finally, evidence supports the efficacy of both oral naltrexone and extended-release injectable naltrexone versus placebo for the treatment of opioid use disorder.[45–47]

Pharmacotherapy Options

The medications covered in this guideline are mainly those that have been approved by the US FDA for the treatment of opioid dependence as defined in prior versions of the DSM-III and DSM-IV, and ''not necessarily'' the definition contained in the current version of the manual, the DSM-5. DSM-5 combined ''opioid abuse'' and ''opioid dependence'' criteria from prior versions of the DSM and included them in the new definition of ''opioid use disorder.'' As a result, pharmacologic treatment may not be appropriate for all patients along the entire opioid use disorder continuum. In a study comparing opioid dependence from DSM-IV and opioid use disorder from DSM-5, optimal concordance occurred when four or more DSM-5 criteria were endorsed (ie, the DSM-5 threshold for moderate opioid use disorder).[8]

The medications discussed in this *Practice Guideline* all have ample evidence supporting their safety and efficacy. It is recognized that other medications have been used off-label to treat opioid use disorder, but with some exceptions (clearly noted in the text) the Guideline Committee has not issued recommendations on the use of these medications. Cost-efficacy was not a consideration in the development of this *Practice Guideline*.

Each medication will be discussed in detail in subsequent sections:

(1) Methadone (mu-agonist) for opioid use disorder treatment and withdrawal management (part 4).

(2) Buprenorphine (partial mu-agonist) for opioid use disorder treatment and withdrawal management (part 5).

(3) Naltrexone (antagonist) for relapse prevention (part 6).

(4) Naloxone (antagonist) to treat overdose (part 13).

The only medication that is ''not'' US FDA-approved for the treatment of opioid use disorder that will be covered in this *Practice Guideline* is the use of the alpha-2 adrenergic agonist, clonidine, for the treatment of opioid withdrawal (see ''Part 3: Treating Opioid Withdrawal'').

Key outcomes in evaluating the efficacy of the various pharmacotherapies include: decreased mortality,

abstinence from opioids, and retention in treatment. In regards to these key outcomes, there is some evidence supporting the relative efficacy of one medication over another, but in many cases, there are no good-quality studies comparing the relative benefits of one medication over another. As noted above, there is strong evidence supporting the superiority of methadone over drug-free treatment for reducing mortality, reducing opioid use, and promoting treatment retention.[48]

Efficacy Considerations

Treatment Setting

In accordance with US Federal laws and regulations derived from the Harrison Act and Congressional exceptions to that 1914 law, the venue in which treatment for opioid use disorder is provided is as important a consideration as is the specific medication selected (methadone vs. buprenorphine vs. naltrexone).[49] Federal and state-licensed OTPs offer daily supervised dosing of methadone. OTPs are state and federally regulated to dispense opioid agonist treatment. An increasing number of such highly regulated programs also offer the option of daily supervised dosing of buprenorphine.

In accordance with Federal law 21 CFR §1306.07, office-based opioid treatment (OBOT), which provides authorization of medication via regular outpatient prescriptions filled in a retail pharmacy like any other prescription medication, is available for buprenorphine, but not for methadone. Physicians in private practices, or various other types of private and public sector clinics, can be authorized to prescribe outpatient supplies of the partial opioid agonist buprenorphine. This flexibility to provide OBOT is discussed more in "Part 5: Buprenorphine." There are no regulations regarding facilities themselves, but rather of the individual physician who prescribes buprenorphine (see "Part 5: Buprenorphine" for physician qualifications associated with OBOT).

Naltrexone can be prescribed in any setting by any clinician with the authority to prescribe any medication. It is not listed among federal or state-controlled substances schedules, and there are no regulations of facilities or prescribers for the use of naltrexone in the treatment of opioid use disorder (such that there are for OTP and OBOT).

It is recommended that the clinician consider a patient's psychosocial situation, co-occurring disorders, and opportunities for treatment retention versus risks of diversion when determining whether OTP or OBOT is most appropriate.

Pharmacology

Differences in efficacy may also arise from differences in pharmacology; whereas methadone is a full agonist at the mu-opioid receptor and produces higher levels of physiological dependence; buprenorphine is a partial agonist with less physiological dependence. There are few studies comparing the relative efficacy of methadone versus buprenorphine in reducing opioid use. Likewise, evidence supports the efficacy of naltrexone for relapse prevention compared to a placebo control.[45,50] There is an absence of studies that compare treatment using either oral naltrexone or extended-release injectable naltrexone versus agonist treatment with either methadone or buprenorphine.

Contraindications and Precautions

The following section describes the major indications, contraindications, and precautions for methadone, buprenorphine, and naltrexone. This section is a summary and is not an exhaustive description of medication information. (Refer to Table 3 below for a summary of contraindications and precautions.)

Methadone

Methadone is frequently used to manage withdrawal symptoms from opioids and is recommended for pharmacological treatment of opioid use disorder (see "Part 4: Methadone").

Methadone is "contraindicated" for the following conditions:

(1) Patients with known hypersensitivity to methadone hydrochloride.
(2) Patients experiencing respiratory depression (in the absence of resuscitative equipment or in unmonitored settings).
(3) Patients with acute bronchial asthma or hypercapnia (also known as hypercarbia).
(4) Patients with known or suspected paralytic ileus.

Methadone should be used with "caution" for the following conditions:

(1) Patients with decompensated liver disease (eg, jaundice, ascites) due to increased risk of hepatic encephalopathy.
(2) Patients with respiratory insufficiency.
(3) Patients with concomitant substance use disorders, particularly patients with sedative, hypnotic, or anxiolytic use disorders. Interactions between methadone and hypnotics, sedatives, or anxiolytics may be life-threatening.
(4) Patients with concomitant psychiatric diagnoses that impair their ability to maintain daily attendance at an OTP.
(5) Patients with low levels of physical dependence to opioids should be started with low doses of methadone.
    Significant "medication interactions" to consider before starting methadone are as follows:

(1) Methadone may prolong the QT interval and should be used in caution with other agents that may also prolong the QT interval. These include class I or class III antiarrhythmic drugs, calcium channel blockers, some antipsychotics, and some antidepressants.
(2) Methadone is metabolized through the cytochrome P450 enzyme pathway. Many agents interact with this pathway including alcohol, anticonvulsants, antiretrovirals, and macrolide antibiotics.

Buprenorphine

Buprenorphine is a partial opioid agonist and mixed opioid agonist–antagonist. It is usually provided in a formulation that includes naloxone. Buprenorphine is recommended

TABLE 3. Contraindications and Precautions for Pharmacotherapy Options

Medication	Contraindications	Warnings and Precautions
Methadone	Hypersensitivity Respiratory depression Severe bronchial asthma or hypercapnia Paralytic ileus	Cardiac conduction effects Diversion and misuse are possible Physical dependence Respiratory depression when used in association with CNS depressants including alcohol, other opioids, and illicit drugs Head injury and increased intracranial pressure Liver disease Respiratory insufficiency Concomitant substance use disorders Co-occurring psychiatric disorders Drug interactions with medications metabolized by cytochrome p450 enzymes principally CYP34A, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9and CYP2D6 Drugs coadministered with methadone should be evaluated for interaction potential
Buprenorphine (all formulations)	Hypersensitivity	Diversion and misuse are possible Physical dependence Respiratory depression when used in association with CNS depressants including alcohol, other opioids, and illicit drugs Precipitated withdrawal if used in patients physically dependent on full agonists opioids before the agonist effects have worn off Neonatal withdrawal has been reported after use of buprenorphine during pregnancy Not recommended for patients with severe hepatic impairment May cause sedation
Naltrexone (oral and injectable formulations)	Hypersensitivity reactions to naltrexone, or for injectable previous hypersensitivity reactions to polylactide-co-glycolide, carboxymethylcellulose, or any other constituent of the diluent Patients currently physically dependent on opioids, including partial agonists Patients receiving opioid analgesics Patients in acute opioid withdrawal	Vulnerability to overdose Injection site reactions associated with injectable naltrexone Precipitated opioid withdrawal Risk of hepatotoxicity Patient should be monitored for the development of depression and suicidality Emergency reversal of opiate blockade may require special monitoring in a critical care setting Eosinophil pneumonia has been reported in association with injectable naltrexone Administer IM injections with caution to patients with thrombocytopenia or a coagulation disorder

IM, intramuscular.

for pharmacological treatment of opioid use disorder (see "Part 5: Buprenorphine").

Buprenorphine is also an effective treatment for opioid withdrawal with efficacy similar to methadone, and much superior to clonidine in opioid withdrawal management.[51–53] Although one trial did find that longer courses of buprenorphine with gradual tapering were superior to rapid tapering for withdrawal,[54] there is insufficient evidence on outcomes to make recommendations on buprenorphine taper duration.

Buprenorphine is "contraindicated" for the following conditions:

(1) Patients with hypersensitivity to buprenorphine or any component of the formulation.
(2) Patients with severe liver impairment are not good candidates for office-based treatment with buprenorphine. (Patients with hepatitis C infection who do not have severe liver impairment may, however, be considered for buprenorphine.)

Buprenorphine should be used with "caution" for the following conditions:

(1) Patients in whom hepatitis has been reported, particularly in patients with previous hepatic dysfunction. A direct comparison of the effects of buprenorphine and methadone, however, showed no evidence of liver damage during the initial 6 months in either treatment groups.[55] Monitoring liver function in patients at increased risk for hepatotoxicity may be considered.
(2) Patients who, at present, have an alcohol use or sedative, hypnotic, or anxiolytic use disorder.
(3) Patients with hypovolemia, severe cardiovascular disease, or taking drugs that may exaggerate hypotensive effects. Buprenorphine may cause hypotension, including orthostatic hypotension and syncope.

Significant "medication interactions" to consider before starting buprenorphine include the following:

(1) Alcohol and sedatives, hypnotics, or anxiolytics may enhance the central nervous system depressive effect of buprenorphine.

(2) Buprenorphine is metabolized to nor-buprenorphine primarily by cytochrome CYP3A4; therefore, potential interactions may occur when buprenorphine is given concurrently with agents that affect CYP3A4 activity. The concomitant use of buprenorphine with CYP3A4 inhibitors (eg, azole antifungals such as ketoconazole, macrolide antibiotics such as erythromycin, and HIV protease inhibitors) should be monitored and may require dose reduction of one or both agents.[56–58]

Naltrexone

Naltrexone is recommended for pharmacological treatment of opioid use disorder (see "Part 6: Naltrexone"). Naltrexone is an opioid antagonist that blocks the effects of opioids. It is a pharmacotherapy option used to treat opioid use disorder and prevent relapse after detoxification. Naltrexone causes immediate withdrawal symptoms (precipitated withdrawal) in a person with active physical dependence on opioids. There are oral and extended-release injectable formulas of naltrexone. Oral naltrexone, if taken daily, is most effective in patients who are highly motivated or legally mandated to receive treatment, and/or when taking the medication is closely supervised. Conversely, the efficacy of oral naltrexone for the treatment of opioid use disorder is often adversely affected by poor medication adherence.[59] Clinicians may want to reserve using oral naltrexone for patients who are able to comply with special techniques to enhance their adherence, for example, observed dosing. An extended-release injectable naltrexone formulation is available, which may overcome the adherence limitations of the oral formulation. This formulation requires a once-monthly injection.

Naltrexone is "contraindicated" under the following conditions:

(1) Patients with hypersensitivity reactions to naltrexone.

(2) Patients who have previously exhibited hypersensitivity to naltrexone, polylactide-co-glycolide, carboxymethyl-cellulose, or any other components of the diluent (for extended-release injectable naltrexone).

(3) Patients with current physical dependence on opioids, including partial agonists.

(4) Patients with current physiologic opioid dependence.

(5) Patients in acute opioid withdrawal.

(6) Any individual who has failed the naloxone challenge test (see "Glossary") or has a positive urine screen for opioids.

Naltrexone should be used with "caution" under the following conditions:

(1) All patients should be warned of the risk of hepatic injury and advised to seek medical attention if they experience symptoms of acute hepatitis. Hepatic injury is a concern if very high doses are used, for example, 200–300 mg per day. Use of naltrexone should be discontinued in the event of symptoms and/or signs of acute hepatitis. Cases of hepatitis and clinically significant liver dysfunction were observed in association with naltrexone exposure during the clinical development program and in the postmarketing period. Transient, asymptomatic hepatic transaminase elevations were also observed in the clinical trials and postmarketing period.

(2) Patients with liver impairment should complete liver enzyme tests before and during treatment with naltrexone to check for additional liver impairment.

(3) Patients who experience injection site reactions should be monitored for pain, redness, or swelling. Incorrect administration may increase the risk of injection site reactions. Reactions have occurred with extended-release injectable naltrexone.

(4) Patients with co-occurring psychiatric disorders should be monitored for adverse events. Suicidal thoughts, attempted suicide, and depression have been reported.

Significant "medication interactions" with naltrexone are as follows:

(1) Naltrexone should not be used with methylnaltrexone or naloxegol.

(2) Naltrexone blocks the effects of opioid analgesics because it is an opioid antagonist.

(3) Glyburide may increase serum concentration of naltrexone. Monitor for increased toxicity effects of naltrexone.

Summary of Recommendations

(1) The choice of available treatment options for addiction involving opioid use should be a shared decision between the clinician and the patient.

(2) Clinicians should consider the patient's preferences, past treatment history, and treatment setting when deciding between the use of methadone, buprenorphine, and naltrexone in the treatment of addiction involving opioid use. The treatment setting described as level 1 treatment in the ASAM Criteria may be a general outpatient location such as a clinician's practice site. The setting as described as level 2 in the ASAM Criteria may be an intensive outpatient treatment or partial hospitalization program housed in a specialty addiction treatment facility, a community mental health center, or another setting. The ASAM Criteria describes level 3 or level 4 treatment, respectively, as a residential addiction treatment facility or hospital.

(3) The venue in which treatment is provided is as important as the specific medication selected. OTPs offer daily supervised dosing of methadone, and increasingly of buprenorphine. In accordance with Federal law (21 CFR §1306.07), OBOT, which provides medication on a prescribed weekly or monthly basis, is limited to buprenorphine.[9] Naltrexone can be prescribed in any setting by any clinician with the authority to prescribe any medication. Clinicians should consider a patient's psychosocial situation, co-occurring disorders, and risk of diversion when determining whether OTP or OBOT is most appropriate.

(4) OBOT may not be suitable for patients with active alcohol use disorder or sedative, hypnotic, or anxiolytic

use disorder (or who are in the treatment of addiction involving the use of alcohol or other sedative drugs, including benzodiazepines or benzodiazepine receptor agonists). It may also be unsuitable for persons who are regularly using alcohol or other sedatives, but do not have addiction or a specific substance use disorder related to that class of drugs. The prescribing of benzodiazepines or other sedative-hypnotics should be used with extreme caution in patients who are prescribed methadone or buprenorphine for the treatment of an opioid use disorder.

(5) Methadone is recommended for patients who may benefit from daily dosing and supervision in an OTP, or for patients for whom buprenorphine for the treatment of opioid use disorder has been used unsuccessfully in an OTP or OBOT setting.

(6) Oral naltrexone for the treatment of opioid use disorder is often adversely affected by poor medication adherence. Clinicians should reserve its use for patients who would be able to comply with special techniques to enhance their adherence, for example, observed dosing. Extended-release injectable naltrexone reduces, but does not eliminate, issues with medication adherence.

Areas for Further Research

More research is needed to compare the advantages of agonists and antagonists in the treatment of opioid use disorder. Whereas methadone, buprenorphine, and naltrexone are all superior to no treatment in opioid use disorder, less is known about their relative advantages.

PART 3: TREATING OPIOID WITHDRAWAL

Background

Opioid withdrawal syndrome refers to the wide range of symptoms that occur after stopping or dramatically reducing the dose of opioid drugs after heavy and prolonged use. For short-acting opioids such as heroin and oxycodone, symptoms usually emerge within 12 hours of the last opioid use, peak within 24–48 hours, and diminish over 3–5 days. For long-acting opioids such as methadone, withdrawal symptoms generally emerge within 30 hours of the last methadone exposure and may last up to 10 days. Although distressing, opioid withdrawal syndrome is rarely life-threatening. However, abrupt discontinuation of opioids is not recommended because it may precipitate withdrawal, lead to strong cravings, and result in relapse to drug use.

Symptoms of opioid withdrawal may include any of the following:

(1) Muscle aches
(2) Increased tearing
(3) Runny nose
(4) Dilated pupils
(5) Piloerection
(6) Agitation
(7) Anxiety

(8) Insomnia
(9) Sweating
(10) Yawning
(11) Abdominal cramping
(12) Nausea
(13) Vomiting
(14) Diarrhea.

Opioid withdrawal generally results from the cessation or a dramatic reduction in the dose of opioids, which is referred to as spontaneous withdrawal. Opioid withdrawal can also be precipitated when a patient who is physically dependent on opioids is administered an opioid antagonist such as naloxone or naltrexone, or an opioid partial agonist such as buprenorphine. Signs and symptoms of precipitated withdrawal are similar to those of spontaneous withdrawal, but the time course is different and symptoms may be much more severe. Review of postmarketing cases of precipitated opioid withdrawal in association with treatment with naltrexone has identified cases with symptoms of withdrawal severe enough to require hospital admission, and in some cases, management in the intensive care unit.[60,61]

The timing of maximal precipitated withdrawal usually occurs in the following scenarios:

(1) Within 1 minute for intravenously administered naloxone.
(2) Several minutes after IM naloxone.
(3) Up to 90 minutes after sublingual buprenorphine.
(4) Up to several hours after extended-release injectable naltrexone.[62]

The duration of the withdrawal depends on the half-life and dose of the partial agonist or antagonist. Naloxone-precipitated withdrawal typically lasts for 30–60 minutes, whereas buprenorphine or naltrexone-precipitated withdrawal may last for several days. The ability to accurately assess patients for opioid withdrawal is important to avoid precipitated withdrawal when introducing antagonists and partial agonists for relapse prevention.

Withdrawal management can make withdrawal from opioids more comfortable. Given the high rate of relapse, opioid withdrawal management is not considered an effective treatment of opioid use disorder on its own.[63] If withdrawal management alone, or withdrawal management followed by psychosocial treatment alone is proposed, the patient should be informed of the estimated risks of subsequent relapse, including the increased risk for death, as compared to treatment with opioid agonists. Withdrawal management is not necessary or recommended for patients being referred for treatment with methadone or buprenorphine.

Assessment of Patient for Opioid Withdrawal

Assessment of a patient undergoing opioid withdrawal should include a thorough medical history and physical examination focusing on signs and symptoms associated with opioid withdrawal. There are various scales available to assess opioid withdrawal. Objective signs, when present, are more reliable, but subjective withdrawal features can also be sensitive measures of opioid withdrawal. These scales may be

used to measure opioid withdrawal symptoms during the initial assessment to make the diagnosis of opioid withdrawal. In addition, clinicians can assess the effectiveness of withdrawal management by repeating these scales intermittently as they treat withdrawal symptoms.

Objective Opioid Withdrawal Scale (OOWS) is an objective measure in which the clinician checks for 13 signs of opioid withdrawal (eg, yawning, perspiration).[38]

Clinical Opioid Withdrawal Scale (COWS) is a clinical assessment for 11 medical signs and symptoms of opioid withdrawal (eg, gastrointestinal distress).[64]

Subjective Opioid Withdrawal Scale (SOWS) is a measure of 16 subjective symptoms of withdrawal, in which the patient rates their experience on a 5-point scale (eg, ''I feel restless'').[38]

Opioid withdrawal management may occur in either inpatient or outpatient settings. There is a lack of evidence to determine the relative safety of inpatient versus outpatient withdrawal management. Inpatient withdrawal management has higher rates of completion compared to outpatient withdrawal management; however, there is no demonstrable difference in relapse among inpatient versus outpatient withdrawal management.[65]

Medications in Opioid Withdrawal

For the management of opioid withdrawal, two main strategies have evolved. The first involves the provision of gradually tapering doses of opioid agonists, typically methadone or buprenorphine. The other strategy is the use of alpha-2 adrenergic agonists (clonidine) along with other non-narcotic medications to reduce withdrawal symptoms. Both strategies have advantages and disadvantages. Using tapering doses of opioid agonists has been shown to be superior to clonidine in terms of retention and opioid abstinence. However, the use of nonopioid medications may be the only option available to clinicians in some healthcare settings and may also facilitate the transition of patients to opioid antagonist medications and help prevent subsequent relapse. Recently, researchers have begun to investigate the use of combinations of buprenorphine and low doses of oral naltrexone to rapidly detoxify patients and facilitate the accelerated introduction of extended-release injectable naltrexone.[19] Although these techniques seem promising, more research will be needed before these can be accepted as standard practice.

Withdrawal Management with Opioid Agonists

Methadone and buprenorphine are both recommended in the management of opioid withdrawal and have comparable results in terms of retention and opioid abstinence. Withdrawal management with methadone must be done in an OTP or inpatient setting. Methadone tapers generally start with doses in the range of 20–30 mg per day, and are completed in 6–10 days.

Buprenorphine withdrawal management can be done either in an outpatient or an inpatient setting. None of the available forms of buprenorphine, including the buprenorphine monoproducts (Suboxone, Zubsolv, and Bunavail), are specifically US FDA-approved for withdrawal management, but may be used for this purpose. None of the products have

shown superiority over another for this purpose. In the remainder of this section, the term buprenorphine refers to the monotherapy and combination formulations.

Buprenorphine is a partial mu-opioid receptor antagonist with a higher affinity for the mu-receptor than most full agonists such as heroin and oxycodone. Therefore, it is important that buprenorphine should not be started until a patient is exhibiting opioid withdrawal to avoid precipitated withdrawal. Usually buprenorphine is not started until 12–18 hours after the last dose of a short-acting agonist such as heroin or oxycodone, and 24–48 hours after the last dose of a long-acting agonist such as methadone. A dose sufficient to suppress withdrawal symptoms is achieved (4–16 mg per day) and then the dose is tapered. The duration of the taper can be as brief as 3–5 days or as long as 30 days or more.

Studies examining the relative efficacy of long versus short-duration tapers are not conclusive, and the Guideline Committee was unable to reach a consensus on this issue. Physicians should be guided by patient response in determining the optimum duration of the taper.

Withdrawal Management with Alpha-2 Adrenergic Agonists

Because opioid withdrawal results largely from overactivity of the brain's noradrenergic system, alpha-2 adrenergic agonists (clonidine, lofexidine) have a long history of off-label use for the treatment of opioid withdrawal in the United States. Lofexidine is approved for the treatment of opioid withdrawal in the United Kingdom. Clonidine is generally used at doses of 0.1–0.3 mg every 6–8 hours, with a maximum dose of 1.2 mg daily. Its hypotensive effects often limit the amount that can be used. Clonidine is often combined with other non-narcotic medications targeting specific opioid withdrawal symptoms such as benzodiazepines for anxiety, loperamide or bismuth-salycilate for diarrhea, acetaminophen or nonsteroidal anti-inflammatory medications (NSAIDs) for pain, various medications for insomnia, and ondansetron for nausea. Other agents in the same pharmacological family as clonidine, such as guanfacine (available in the United States) and lofexidine (available in many other countries) can be used off-label as safe and effective agents in the management of opioid withdrawal.

Anesthesia-Assisted Withdrawal Management

Anesthesia-assisted opioid detoxification or ultra-rapid opioid detoxification (UROD) uses large doses of naloxone to precipitate acute opioid withdrawal in the patient who is under general anesthesia. Patients are anesthetized, then intubated and mechanically ventilated. A diuretic is used to enhance excretion of the opioid. Patients experience mild withdrawal symptoms for about 6 days after awakening from anesthesia, compared with similar withdrawal symptoms on a 20-day methadone taper.[66,67]

The ASAM recommends against the use of UROD in the treatment of opioid withdrawal and stated these same recommendations in a policy statement.[68] ASAM's position is in accordance with other guidelines. Serious complications including cardiac arrest and death have been reported with anesthesia-assisted withdrawal management.[69] The Centers for

Disease Control issued a warning in 2013 about severe adverse events including death from anesthesia-assisted withdrawal management.[70] Furthermore, a systematic review of five randomized trials concluded that the lack of benefit, potential serious harms, and costs of heavy sedation or anesthesia do not support its use.[71]

Summary of Recommendations

(1) Using medications for opioid withdrawal management is recommended over abrupt cessation of opioids. Abrupt cessation of opioids may lead to strong cravings, which can lead to continued use.

(2) Patients should be advised about risk of relapse and other safety concerns from using opioid withdrawal management as standalone treatment for opioid use disorder. Opioid withdrawal management on its own is not a treatment method.

(3) Assessment of a patient undergoing opioid withdrawal management should include a thorough medical history and physical examination focusing on signs and symptoms associated with opioid withdrawal.

(4) Opioid withdrawal management in cases in which methadone is used to manage withdrawal symptoms must be done in an inpatient setting or in an OTP. For short-acting opioids, tapering schedules that decrease in daily doses of prescribed methadone should begin with doses between 20 and 30 mg per day, and should be completed in 6–10 days.

(5) Opioid withdrawal management in cases in which buprenorphine is used to manage withdrawal symptoms should not be initiated until 12–18 hours after the last dose of a short-acting agonist such as heroin or oxycodone, and 24–48 hours after the last dose of a long-acting agonist such as methadone. A dose of buprenorphine sufficient to suppress withdrawal symptoms is given (this can be 4–16 mg per day) and then the dose is tapered. The duration of the tapering schedule can be as brief as 3–5 days or as long as 30 days or more.

(6) The use of combinations of buprenorphine and low doses of oral naltrexone to manage withdrawal and facilitate the accelerated introduction of extended-release injectable naltrexone has shown promise. More research will be needed before this can be accepted as standard practice.

(7) The Guideline Committee recommends, based on consensus opinion, the inclusion of clonidine as a recommended practice to support opioid withdrawal. Clonidine is not US FDA-approved for the treatment of opioid withdrawal, but it has been extensively used off-label for this purpose. Clonidine may be used orally or transdermally at doses of 0.1–0.3 mg every 6–8 hours, with a maximum dose of 1.2 mg daily to assist in the management of opioid withdrawal symptoms. Its hypotensive effects often limit the amount that can be used. Clonidine can be combined with other non-narcotic medications targeting specific opioid withdrawal symptoms such as benzodiazepines for anxiety, loperamide for diarrhea, acetaminophen or NSAIDs for pain, and ondansetron or other agents for nausea.

(8) Opioid withdrawal management using anesthesia UROD is not recommended due to high risk for adverse events or death. Naltrexone-facilitated opioid withdrawal management can be a safe and effective approach, but should be used only by clinicians experienced with this clinical method and in cases in which anesthesia or conscious sedation are not being employed.

Areas for Further Research

(1) Further research is needed to evaluate the efficacy and safety of alpha-2 adrenergic and other nonopioid medications that are being used off-label for withdrawal management. These nonopioid medications may have use in transitioning patients onto antagonists for relapse prevention.

(2) Further study is needed on other methods to accelerate the withdrawal process and facilitate the introduction of antagonists.

(3) More research is needed to make recommendations on the optimal duration of a buprenorphine taper.

(4) More research is needed to evaluate the safety of inpatient as compared to outpatient withdrawal management.

(5) More research is needed to compare the effectiveness of short versus long tapers with buprenorphine withdrawal management.

PART 4: METHADONE

Background

Methadone (Dolophine or Methadose) is a slow-acting opioid agonist. Methadone is an effective treatment for opioid withdrawal management and the treatment of opioid use disorder. Methadone is taken orally so that it reaches the brain slowly, dampening the euphoria that occurs with other routes of administration while preventing withdrawal symptoms. Methadone has been used since the 1960s to treat heroin addiction and remains an effective treatment option. Many studies have demonstrated its superiority to using abstinence-based approaches.[41] Methadone is only available through approved OTPs, where it is dispensed to patients on a daily or almost daily basis in the initial stages of treatment. Federal and State laws allow take-home doses for patients who have demonstrated treatment progress and are judged to be at low risk for diversion.

Patient Selection and Treatment Goals

Treatment with methadone at an OTP is recommended for patients who have opioid use disorder, are able to give informed consent, and have no specific contraindications for agonist treatment. Treatment with methadone has the following four goals:

(1) To suppress opioid withdrawal.
(2) To block the effects of illicit opioids.
(3) To reduce opioid craving and stop or reduce the use of illicit opioids.
(4) To promote and facilitate patient engagement in recovery-oriented activities including psychosocial intervention.

Precautions

Arrhythmias

Patients should be informed of the potential risk of arrhythmia when they are dispensed methadone. It is

recommended to get a history of structural heart disease, arrhythmia, or syncope. In addition, the clinician should assess the patient for other risk factors for QT-interval prolongation. An electrocardiogram (ECG) should be considered when high doses of methadone (over 120 mg per day) are being employed, there is a history of prolonged QT interval, or the patient is taking medications known to prolong the QT. However, there is no research on the use of ECG data for improving patient outcomes.

Course of Treatment

Induction

Initial dosing depends on the level of physical dependence. Consequently, induction varies widely. In a recent publication prepared by ASAM's Methadone Action Group, the recommended initial dose ranges from 10 to 30 mg, with reassessment in 2–4 hours when peak levels have been reached.[72]

Given the risk of overdose in the first 2 weeks, tolerance is an important safety consideration. Federal law mandates that the initial dose cannot exceed 30 mg and not exceed 40 mg in 1 day.[39]

Dosing

Methadone has a long half-life and care must be taken to avoid too rapid dose increases during the first 1–3 weeks of treatment so as to avoid increasing the dose before the full effect of the last dose has been realized. Dosing should be based on patients achieving goals of treatment, can vary widely between patients, and doses do not correlate well with blood levels. Trough and peak plasma levels of methadone (or methadone blood levels) may be used in addition to clinical evaluation to assess the safety and adequacy of a patient's dose, particularly in patients who seem to be rapid metabolizers and may need a split dose.[15,73–76] A relatively low dose of methadone (eg, <30 mg per day) can lessen acute opioid withdrawal, but is often not effective in suppressing craving and blocking the effects of other opioids. Most patients fare better on methadone doses between 60 and 120 mg per day, which typically creates sufficient tolerance to minimize a euphoric response if patients self-administer additional opioids.

A relatively low dose of methadone (eg, <30 mg per day) can lessen acute withdrawal, but is often not effective in suppressing craving and blocking the effects of other opioids. Though a few patients respond to a maintenance dose of 30–60 mg per day, most patients fare better if their initial 30–40 mg per day dose is gradually raised to a maintenance level of 60–120 mg per day, which typically creates sufficient tolerance to minimize a euphoric response if patients self-administer additional opioids. Multiple randomized trials have found that patients have better outcomes, including retention in treatment, with higher doses (80–100 mg per day) than lower doses.[77,78] Though not well studied, doses above 120 mg per day are being used with some patients as blockade of opioid effects is becoming increasingly more difficult due to the increased purity of heroin and strength of prescription opioids.[72]

Adverse Effects

Higher methadone doses may be associated with increased risk of adverse effects, including prolongation of the QT interval and other arrhythmias (torsades des pointes), which in some cases have been fatal.[79] The US FDA issued a safety alert for methadone regarding these cardiac events.[80] Clinicians, in consultation with patients, may need to consider the relative risk of adverse events due to QT prolongation with methadone as compared to the risk of morbidity and mortality of an untreated opioid use disorder.[81] Changing to buprenorphine or naltrexone maintenance should be considered when risks of QT prolongation are high as they do not seem to significantly prolong the QT.

Psychosocial Treatment

Because opioid use disorder is a chronic relapsing disease, strategies specifically directed at relapse prevention are an important part of comprehensive outpatient treatment and should include drug counseling and/or other psychosocial treatments. However, there may be instances when pharmacotherapy alone results in an excellent outcome.

Family involvement in treatment provides strong support for patient recovery; and family members also benefit. The concept of "family" should be expanded to include members of the patient's social network (as defined by the patient), including significant others, clergy, employers, and case managers.

Monitoring Treatment

Federal and state-approved OTPs dispense methadone and supervise administration. Treatment should include relapse monitoring with frequent testing for alcohol and other relevant psychoactive substances. Testing for methadone and buprenorphine is recommended to ensure adherence and detect possible diversion.

Length of Treatment

The optimal duration of treatment with methadone has not been established; however, it is known that relapse rates are high for most patients who drop out; thus long-term treatment is often needed. Treatment duration depends on the response of the individual patient and is best determined by collaborative decisions between the clinician and the patient. Treatment should be reinstituted immediately for most patients who were previously taking methadone and have relapsed or are at risk for relapse.

Switching Treatment Medications

Switching from methadone to other opioid treatment medications may be appropriate in the following cases:

(1) Patient experiences intolerable methadone side effects.
(2) Patient has not experienced a successful course of treatment on methadone.
(3) Patient wants to change and is a candidate for the alternative treatment.

Transfer of medications should be planned, considered, and monitored. Particular care should be taken in reducing

methadone dosing before transfer to avoid precipitating a relapse. If the patient becomes unstable and appears at risk for relapse during the transfer of medications, reinstating methadone may be the best option.

Switching to Buprenorphine

Patients on low doses of methadone (30–40 mg per day or less) generally tolerate the transition to buprenorphine with minimal discomfort; whereas patients on higher doses of methadone may find that switching causes significant discomfort. Patients should be closely monitored during such a switch because there is a risk that stable methadone patients may become unstable when changing to buprenorphine.

To minimize the risk of precipitated withdrawal, it is recommended that physicians use careful initial dosing followed by rapid titration up to an appropriate maintenance dose. Because of concern that sublingually-absorbed naloxone could increase the risk of precipitated withdrawal, treatment initiation with buprenorphine monoproduct is recommended for patients transitioning from methadone and any other long-acting opioid. Patients should be experiencing mild to moderate opioid withdrawal before the switch. This would typically occur at least 24 hours after the last dose of methadone, and indicates that sufficient time has elapsed for there to be minimal risk that the first dose of buprenorphine will precipitate significant withdrawal. Moderate withdrawal would equate to a score greater than 12 on the COWS.[64]

An initial dose of 2–4 mg of buprenorphine should be given and the patient should be observed for 1 hour. If withdrawal symptoms improve, the patient can be dispensed two additional 2–4-mg doses to be taken as needed. The prescribing doctor should contact the patient later in the day to assess the response to dosing. The likelihood of precipitating withdrawal on commencing buprenorphine is reduced as the time interval between the last methadone dose and the first buprenorphine dose increases.

Switching to Naltrexone

Patients switching from methadone to oral naltrexone or extended-release injectable naltrexone need to be completely withdrawn from methadone and other opioids before they can receive naltrexone. This may take up to 14 days, but can typically be achieved in 7 days.[82] A naloxone challenge (administration of 0.4–0.8 mg naloxone and observation for precipitated withdrawal) may be useful before initiating treatment with naltrexone to document the absence of physiological dependence and to minimize the risk for precipitated withdrawal (see ''Glossary'' for more on naloxone challenge).

Summary of Recommendations

(1) Methadone is a treatment option recommended for patients who are physiologically dependent on opioids, able to give informed consent, and who have no specific contraindications for agonist treatment when it is prescribed in the context of an appropriate plan that includes psychosocial intervention.

(2) The recommended initial dose ranges for methadone are from 10 to 30 mg, with reassessment in 3–4 hours and a second dose not to exceed 10 mg on the first day if withdrawal symptoms are persisting.

(3) The usual daily dosage of methadone ranges from 60 to 120 mg. Some patients may respond to lower doses and some may need higher doses. Dosage increases in 5–10-mg increments applied no more frequently than every 7 days (depending on clinical response) are necessary to avoid oversedation, toxicity, or even iatrogenic overdose deaths.

(4) The administration of methadone should be monitored because unsupervised administration can lead to misuse and diversion. OTP regulations require monitored medication administration until the patient's clinical response and behavior demonstrate that the prescribing of nonmonitored doses is appropriate.

(5) Psychosocial treatment, though sometimes minimally needed, should be implemented in conjunction with the use of methadone in the treatment of opioid use disorder.

(6) Methadone should be reinstituted immediately if relapse occurs, or when an assessment determines that the risk of relapse is high for patients who previously received methadone in the treatment of opioid use disorder, but who are no longer prescribed such treatment.

(7) Strategies directed at relapse prevention are an important part of comprehensive addiction treatment and should be included in any plan of care for a patient receiving active opioid treatment or ongoing monitoring of the status of their addictive disease.

(8) Switching from methadone to another medication for the treatment of opioid use disorder may be appropriate if the patient experiences intolerable side effects or is not successful in attaining or maintaining treatment goals through the use of methadone.

(9) Patients switching from methadone to buprenorphine in the treatment of opioid use disorder should be on low doses of methadone before switching medications. Patients on low doses of methadone (30–40 mg per day or less) generally tolerate transition to buprenorphine with minimal discomfort, whereas patients on higher doses of methadone may experience significant discomfort in switching medications.

(10) Patients switching from methadone to oral naltrexone or extended-release injectable naltrexone must be completely withdrawn from methadone and other opioids, before they can receive naltrexone. The only exception would apply when an experienced clinician receives consent from the patient to embark on a plan of naltrexone-facilitated opioid withdrawal management.

(11) Patients who discontinue agonist therapy with methadone or buprenorphine and then resume opioid use should be made aware of the risks associated with opioid overdose, and especially the increased risk of death.

Areas for Further Research

(1) Further research is needed to assess the effectiveness of added psychosocial treatment to treatment with methadone in OTP or inpatient settings. Treatment with methadone generally includes some psychosocial components.

However, it is unclear whether added psychosocial treatment improves patient outcomes.

(2) Research is needed to evaluate the use of ECG in treatment with methadone in preventing adverse events.

PART 5: BUPRENORPHINE

Background

Buprenorphine is recommended for the treatment of opioid use disorder. Buprenorphine relieves drug cravings without producing the euphoria or dangerous side effects of other opioids. In addition to its pharmacological properties, an important feature of buprenorphine is its ability to be prescribed in office-based treatment settings. The US FDA approved buprenorphine in 2002, making it the first medication eligible to be prescribed by certified physicians through the Drug Addiction Treatment Act of 2000 (DATA 2000). Through DATA 2000, physicians may apply for waivers to prescribe certain narcotic schedule III, IV, or V medications, including buprenorphine, from their office settings. This provision of the act expands accessibility of community-based treatment options and mitigates the need to receive treatment through more specialized, and often less available, OTPs. However, buprenorphine may also be administered in an OTP setting with structure and administration requirements identical to those for methadone.

Formulations of Buprenorphine

For this *Practice Guideline*, recommendations using the term "buprenorphine" will refer generally to both the buprenorphine only and the combination buprenorphine/naloxone formulations. When recommendations differ by product, the type of product will be described. The monoproduct (generic name buprenorphine) will be referred to as "buprenorphine monoproduct." The combination product will be referred to as "combination buprenorphine/naloxone."

This *Practice Guideline* recommends using combination buprenorphine/naloxone for withdrawal management and treatment of opioid use disorder, with the exception of treatment for pregnant women. (Buprenorphine monoproduct is recommended for pregnant women, because naloxone in the combination product is not recommended for use by pregnant women.) (See "Part 8: Special Populations: Pregnant Women.")

Combination buprenorphine contains naloxone (an opioid antagonist), which is included to discourage intravenous misuse of buprenorphine. If a patient who is physically dependent on a full agonist opioid injects buprenorphine/naloxone, the naloxone will induce withdrawal symptoms. These withdrawal symptoms are averted when buprenorphine/naloxone is taken sublingually as prescribed.

A combination product of buprenorphine and naloxone (Suboxone, Zubsolv, Bunavail) is taken sublingually or in a buccal film. The US FDA-approved generic forms of buprenorphine/naloxone sublingual tablets and buprenorphine monoproduct provide a broader array of treatment options.

The ratio of buprenorphine to naloxone in Suboxone is 4 : 1, and a variety of dose sizes are available (eg, 2/0.5, 4/1, 8/2). Other formulations of buprenorphine/naloxone (Zubsolv, Bunavail) have different bioavailability and have different buprenorphine/naloxone dose strengths. The approved doses of Zubsolv and Bunavail are bioequivalent to the doses of Suboxone discussed in this guideline. Bioequivalence information and charts are contained in Appendix II.

All information provided in this section is based on dosages for the generic equivalents of buprenorphine/naloxone sublingual tablets and buprenorphine sublingual tablets. Because of the possibility of slight differences in bioavailability between the different formulations of buprenorphine, patients switching from one form of buprenorphine to another should be monitored for adverse effects.

Patient Selection and Treatment Goals

Buprenorphine is an effective treatment recommended for patients who have opioid use disorder, are able to give informed consent, and have no specific contraindications for agonist treatment. Treatment with buprenorphine has the following four goals:

(1) To suppress opioid withdrawal.
(2) To block the effects of illicit opioids.
(3) To reduce opioid craving and stop or reduce the use of illicit opioid.
(4) To promote and facilitate patient engagement in recovery-oriented activities including psychosocial intervention.

There is ample evidence for the efficacy of buprenorphine for the treatment of opioid use disorder.[83] The risk of lethal overdose in an opioid-tolerant individual on buprenorphine is substantially less than that associated with the use of other opioid medications such as methadone. This is due to the ceiling effects of buprenorphine across a wide range of doses. Consequently, buprenorphine has been approved for OBOT.

Precautions

Alcohol or Sedative, Hypnotic, or Anxiolytic Use

Some studies have shown potential adverse interactions between buprenorphine and sedatives. Therefore, patients with opioid use disorder and concurrent alcohol, sedative, hypnotic, or anxiolytic use disorders should receive more intensive monitoring during office-based treatment with buprenorphine to minimize the risk of adverse events. Alternatively, patients with these co-occurring disorders may be better treated in a setting with greater supervision such as an OTP.

Course of Treatment

The DATA 2000[9] allows physicians who are trained or experienced in opioid addiction treatment to obtain waivers to prescribe certain schedule III, IV, or V narcotic drugs in the Controlled Substances Act, for the treatment of opioid dependence in their office practices or in a clinic setting. Both buprenorphine monoproduct and combination buprenorphine/naloxone are approved by the US FDA for the treatment of opioid dependence and can be used in settings outside of an OTP. Physicians who wish to prescribe buprenorphine monoproduct or combination buprenorphine/naloxone for the treatment of opioid use disorder or withdrawal management must qualify for a waiver under DATA 2000. Physicians with

approved DATA 2000 waivers are not confined to the office-based setting. Physicians with DATA 2000 waivers may treat opioid addiction with approved buprenorphine products in any outpatient practice settings in which they are otherwise credentialed to practice and in which such treatment would be medically appropriate. This flexibility for place of services is referred to as OBOT. Physicians who qualify for DATA 2000[9] waivers are initially limited in the number of patients they can treat, but after 1 year may apply for a waiver to treat more (see ''Exhibit 4: Physician Qualifications for OBOT'').

Exhibit 4: Physician Qualifications for OBOT

To qualify for a DATA 2000 waiver, a physician must hold a current, valid state medical license and a drug enforcement agency (DEA) registration number.

In addition, the physician must meet at least one of the following criteria outlined by the US Department of Health and Human Services, Substance Abuse, and Mental Health Services Administration:

(1) The physician holds a subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties.
(2) The physician holds an addiction certification from the ASAM. (ASAM certification was taken over by the American Board of Addiction Medicine (ABAM) in 2007.)
(3) The physician holds a subspecialty board certification in addiction medicine from the American Osteopathic Association.
(4) The physician has, with respect to the treatment and management of opioid-addicted patients, completed not less than 8 hours of training (through classroom situations, seminars at professional society meetings, electronic communications, or otherwise) that is provided by the ASAM, the American Academy of Addiction Psychiatry, the American Medical Association, the American Osteopathic Association, the American Psychiatric Association, or any other organization that the Secretary determines is appropriate for purposes of this subclause.
(5) The physician has participated as an investigator in one or more clinical trials leading to the approval of a narcotic drug in schedule III, IV, or V for maintenance or detoxification treatment, as demonstrated by a statement submitted to the Secretary by the sponsor of such approved drug.
(6) The physician has such other training or experience as the State medical licensing board (of the State in which the physician will provide maintenance or detoxification treatment) considers to demonstrate the ability of the physician to treat and manage opioid-addicted patients.
(7) The physician has such other training or experience as the Secretary considers to demonstrate the ability of the physician to treat and manage opioid-addicted patients. Any criteria of the Secretary under this subclause shall be established by regulation. Any such criteria are effective only for 3 years after the date on which the criteria are promulgated, but may be extended for such additional discrete 3-year periods as the Secretary considers appropriate for purposes of this subclause. Such an extension of criteria may only be effectuated through a statement published in the Federal Register by the Secretary during the 30-day period preceding the end of the 3-year period involved.

More detailed information can be found at the web site: http://buprenorphine.samhsa.gov/waiver_qualifications.html

Induction

The buprenorphine monoproduct and Suboxone film are the only medications approved by the US FDA for induction. However, other forms of the combination product have been used by clinicians in patients addicted to short-acting opioids without other complications. Because of concern that sublingually-absorbed naloxone could increase the risk of precipitated withdrawal, treatment initiation with buprenorphine monoproduct is recommended for patients transitioning from methadone and any other long-acting opioid, and patients with hepatic impairment.

Buprenorphine has a higher affinity for the mu-opioid receptor compared to most full opioid agonists. Because buprenorphine is a partial mu-agonist, the risk of overdose during buprenorphine induction is low. However, buprenorphine will displace full agonists from the receptor with resultant reduction in opioid effects. Thus, some patients may experience precipitated withdrawal if insufficient time has elapsed since their last dose of opioids.

Patients should wait until they are experiencing mild to moderate opioid withdrawal before taking the first dose of buprenorphine to reduce the risk of precipitated withdrawal. Generally, buprenorphine initiation should occur at least 6–12 hours after the last use of heroin or other short-acting opioids, or 24–72 hours after their last use of long-acting opioids such as methadone. The use of the COWS can be helpful in determining if patients are experiencing mild to moderate withdrawal.[64] A COWS score of 11–12 or more (mild to moderate withdrawal) is indicative of sufficient withdrawal to allow a safe and comfortable induction onto buprenorphine.

Induction within the clinician's office is recommended to reduce the risk of precipitated opioid withdrawal. Office-based induction is also recommended if the patient or physician is unfamiliar with buprenorphine. However, buprenorphine induction may be done by patients within their own homes.[84] Home-based induction is recommended only if the patient or prescribing physician is experienced with the use of buprenorphine. The recommendation supporting home induction is based on the consensus opinion of the Guideline Committee.

Dosing

At Induction

The risk of precipitated withdrawal can be reduced by using a lower initial dose of buprenorphine. It is recommended that induction start with a dose of 2–4 mg, and that the patient is observed for signs of precipitated withdrawal. If 60–90 minutes have passed without the onset of withdrawal symptoms, then additional dosing can be done in increments of 2–4 mg. Repeat of the COWS during induction can be useful in assessing the effect of buprenorphine doses. Once it has been established that

the initial dose is well tolerated, the buprenorphine dose can be increased fairly rapidly to a dose that provides stable effects for 24 hours and is clinically effective.

After Induction

On average, buprenorphine doses after induction and titration are usually at least 8 mg per day. However, if patients are continuing to use opioids, consideration should be given to increasing the dose by 4–8 mg (daily dose of 12–16 mg or higher). The US FDA approves dosing to a limit of 24 mg per day, and there is limited evidence regarding the relative efficacy of higher doses. In addition, the use of higher doses may increase the risk of diversion.

Adverse Effects

Buprenorphine and combinations of buprenorphine and naloxone are generally well tolerated. Side effects reported with these medications include headache, anxiety, constipation, perspiration, fluid retention in lower extremities, urinary hesitancy, and sleep disturbance. Unlike treatment with methadone, QT-interval prolongation does not seem to be an adverse effect associated with treatment with buprenorphine.

Psychosocial Treatment

Psychosocial treatment is recommended for all patients. The types and duration of psychosocial treatment will vary, and the topic is discussed further in "Part 7: Psychosocial Treatment in Conjunction With Medications for the Treatment of Opioid Use Disorder."

Monitoring Treatment

Patients should be seen frequently at the beginning of their treatment. Weekly visits (at least) are recommended until patients are determined to be stable. The stability of a patient is determined by an individual clinician based on a number of indicators which may include abstinence from illicit drugs, participation in psychosocial treatment and other recovery-based activities, and good occupational and social functioning. Stable patients can be seen less frequently but should be seen at least monthly.

Accessing PDMP data is advisable to check for other medications that the patient may be receiving. Due to the variation in state PDMP laws, clinicians are encouraged to be familiar with the legal requirements associated with PDMPs and prescribing of controlled substances in their state (see "Exhibit 2" in "Part 1: Assessment and Diagnosis of Opioid Use Disorder"). In addition, objective measurement of body fluids for the presence of buprenorphine and illicit drugs of misuse is recommended.

Urine drug testing is a reasonably practical and reliable method to test for buprenorphine and illicit drugs. However, other reliable biological tests for the presence of drugs may be used. It is recommended that patients be tested often and that testing should be done for buprenorphine, substances such as heroin and marijuana, and prescription medications including benzodiazepines, prescription opioids, and amphetamines. How often and exactly what drugs should be tested for to optimize treatment has not been definitively established and is a topic that should be researched further (please see "Drug Testing a White Paper of the American Society of Addiction Medicine for detail on types of drug testing").[40]

Clinicians should take steps to reduce the chance of diversion. Diversion has been reported with buprenorphine monotherapy and combination buprenorphine/naloxone.[85] Strategies to reduce the potential of diversion include: frequent office visits, urine drug testing including testing for buprenorphine and metabolites, observed dosing, and recall visits for pill counts. Patients receiving treatment with buprenorphine should be counseled to have adequate means to secure their medications to prevent theft. Unused medication should be disposed of safely.[86]

Length of Treatment

There is no recommended time limit for treatment with buprenorphine. Buprenorphine taper and discontinuation is a slow process and close monitoring is recommended. Buprenorphine tapering is generally accomplished over several months. Patients and clinicians should not take the decision to terminate treatment with buprenorphine lightly. Factors associated with successful termination of treatment with buprenorphine are not well described, but may include the following:

(1) Employment, engagement in mutual help programs, or involvement in other meaningful activities.
(2) Sustained abstinence from opioid and other drugs during treatment.
(3) Positive changes in the psychosocial environment.
(4) Evidence of additional psychosocial supports.
(5) Persistent engagement in treatment for ongoing monitoring past the point of medication discontinuation.

Patients who relapse after treatment has been terminated should be returned to treatment with buprenorphine.

Switching Treatment Medications

Buprenorphine is generally tolerated well by patients. Switching from buprenorphine to other opioid treatment medications may be appropriate in the following cases:

(1) Patient experiences intolerable side effects.
(2) Patient has not experienced a successful course of treatment in attaining or maintaining goal through the initially chosen pharmacotherapy option.
(3) Patient requires a greater level of supervision or services than office-based buprenorphine offers.
(4) Patient wants to change and is a candidate for treatment.

Switching to Naltrexone

Buprenorphine has a long half-life; 7–14 days should elapse between the last dose of buprenorphine and the start of naltrexone to ensure that the patient is not physically dependent on opioids before starting naltrexone. It may be useful to conduct a naloxone challenge (see "Glossary") before starting naltrexone to demonstrate an absence of physical dependence. Recently, investigators have begun to evaluate newer methods of rapidly transitioning patients from buprenorphine to naltrexone using repeated dosing over several days with very low doses of naltrexone along with ancillary medications.[87]

Although the results are promising, it is too early to recommend these techniques for general practice, and the doses of naltrexone used may not be readily available to most clinicians.

Switching to Methadone

Transitioning from buprenorphine to methadone is less problematic because the addition of a full mu-opioid agonist to a partial agonist does not typically result in any type of adverse reaction. There is no time delay required in transitioning a patient from buprenorphine to treatment with methadone.

Summary of Recommendations

(1) Opioid-dependent patients should wait until they are experiencing mild to moderate opioid withdrawal before taking the first dose of buprenorphine to reduce the risk of precipitated withdrawal. Generally, buprenorphine initiation should occur at least 6–12 hours after the last use of heroin or other short-acting opioids, or 24–72 hours after their last use of long-acting opioids such as methadone.

(2) Induction of buprenorphine should start with a dose of 2–4 mg. Dosages may be increased in increments of 2–4 mg.

(3) Clinicians should observe patients in their offices during induction. Emerging research, however, suggests that many patients need ''not'' be observed and that home buprenorphine induction may be considered. Home-based induction is recommended only if the patient or prescribing physician is experienced with the use of buprenorphine. This is based on the consensus opinion of the Guideline Committee.

(4) Buprenorphine doses after induction and titration should be, on average, at least 8 mg per day. However, if patients are continuing to use opioids, consideration should be given to increasing the dose by 4–8 mg (daily doses of 12–16 mg or higher). The US FDA approves dosing to a limit of 24 mg per day, and there is limited evidence regarding the relative efficacy of higher doses. In addition, the use of higher doses may increase the risk of diversion.

(5) Psychosocial treatment should be implemented in conjunction with the use of buprenorphine in the treatment of opioid use disorder.

(6) Clinicians should take steps to reduce the chance of buprenorphine diversion. Recommended strategies include frequent office visits (weekly in early treatment), urine drug testing including testing for buprenorphine and metabolites, and recall visits for pill counts.

(7) Patients should be tested frequently for buprenorphine, other substances, and prescription medications. Accessing PDMP data may be useful for monitoring.

(8) Patients should be seen frequently at the beginning of their treatment. Weekly visits (at least) are recommended until patients are determined to be stable. There is no recommended time limit for treatment.

(9) Buprenorphine taper and discontinuation is a slow process and close monitoring is recommended. Buprenorphine tapering is generally accomplished over several months. Patients should be encouraged to remain in treatment for ongoing monitoring past the point of discontinuation.

(10) When considering a switch from buprenorphine to naltrexone, 7–14 days should elapse between the last dose of buprenorphine and the start of naltrexone to ensure that the patient is not physically dependent on opioids before starting naltrexone.

(11) When considering a switch from buprenorphine to methadone, there is no required time delay because the addition of a full mu-opioid agonist to a partial agonist does not typically result in any type of adverse reaction.

(12) Patients who discontinue agonist therapy and resume opioid use should be made aware of the risks associated with an opioid overdose, and especially the increased risk of death.

Areas for Further Research

Further research is needed to evaluate the safety and efficacy of buprenorphine induction conducted in the patient's own home, although current research supports this practice in select cases.

PART 6: NALTREXONE

Background

Naltrexone is a long-acting opioid antagonist that may be used to prevent relapse to opioid use. Naltrexone blocks the effects of opioids if they are used. Naltrexone is available in oral (ReVia, Depade) and extended-release injectable (Vivitrol) formulations.

Formulations of Naltrexone: Oral Versus Extended-Release Injectable

Most studies that found oral naltrexone effective were conducted in situations in which patients were highly motivated, were legally mandated to receive treatment, and/or taking the medication under the supervision of their family or significant others. A meta-analysis of 1158 participants in 13 randomized trials compared treatment with oral naltrexone to either placebo or no medication for opioid use disorder.[88] The evidence generated from these trials was limited by poor adherence and high dropout rates. Oral naltrexone was more efficacious than placebo in sustaining abstinence in three trials in which patients had external mandates (eg, legal requirements) and were monitored in adhering to daily doses of the medication.[88,89]

An extended-release injectable naltrexone formulation is available for patients with difficulty adhering to daily medication. This formulation requires an injection once per month. Extended-release injectable naltrexone has been found to be more efficacious than placebo for opioid dependence in randomized trials, although the trials were limited by high dropout rates of about 45% observed at 6 months.[50] One trial found naltrexone to be efficacious in patients with more than one substance use disorder and using more than one drug (heroin and amphetamines), which is a drug combination common in patients with opioid use disorder.[90]

Patient Selection and Treatment Goals

Oral naltrexone and extended-release injectable naltrexone are efficacious treatments recommended for patients who have an opioid use disorder, are able to give informed consent, and have no specific contraindications for agonist treatment. The 1-month protection from relapse after a single dose may make it particularly useful in preventing overdoses and facilitating entry into longer-term treatment if given to prisoners shortly before re-entry or to patients who are discharged from general hospitals after being detoxified in the course of treatment for medical or surgical problems.

Treatment with naltrexone generally has the following four goals:

(1) To prevent relapse to opioids in patients who have already been detoxified and are no longer physically dependent on opioids.
(2) To block the effects of illicit opioids.
(3) To reduce opioid craving.
(4) To promote and facilitate patient engagement in recovery-oriented activities including psychosocial intervention.

Oral Naltrexone

Because oral naltrexone has high rates of nonadherence and the potential for overdose upon relapse, this treatment is best for candidates who can be closely supervised and who are highly motivated. There is a risk of opioid overdose if the patient ceases naltrexone and then uses opioids. Groups that may benefit from oral naltrexone include employed patients, those who have been using drugs for only a short time (eg, younger patients), and those under threat of legal sanctions.

Extended-Release Injectable Naltrexone

Extended-release injectable naltrexone is also an efficacious treatment for opioid use disorder. It may be especially useful for patients who have contraindications to, or who failed pharmacotherapy with buprenorphine and methadone; patients confined to drug-free environments such as prison or inpatient rehabilitation; patients living in areas where agonist treatment is not available; individuals who are highly motivated and are willing to taper off their current agonist therapy; or patients who simply do not want to be treated with an agonist. Because it is US FDA-approved for the treatment of alcohol use disorder, it may be well suited for patients with co-occurring opioid and alcohol use disorders.

Precautions

Risk of Relapse and Subsequent Opioid Overdose

Patients maintained on naltrexone will have diminished tolerance to opioids and may be unaware of the consequent increased sensitivity to opioids if they stop taking naltrexone. Patients who discontinue antagonist therapy should be made aware of this phenomenon. If the patient stops naltrexone and resumes use of opioids in doses similar to those that were being used before the start of treatment with naltrexone, there is risk of an opioid overdose. This is due to the loss of tolerance to opioids and a resulting misjudgment of dose at the time of relapse.[91] A similar dynamic occurs in patients who detoxify

with no meaningful follow-up treatment, or those who drop out of methadone or buprenorphine maintenance.

Course of Treatment

Induction

Before administering naltrexone, it is important that the patient has been adequately detoxified from opioids and is no longer physically dependent. Naltrexone can precipitate severe withdrawal symptoms in patients who have not been adequately withdrawn from opioids. As a general rule, patients should be free from short-acting opioids for about 6 days before starting naltrexone, and free from long-acting opioids such as methadone and buprenorphine for 7–10 days. A naloxone challenge can be used if it is uncertain whether the patient is no longer physically dependent on opioids. In the naloxone challenge, naloxone hydrochloride (a shorter-acting injectable opioid antagonist) is administered and the patient is monitored for signs and symptoms of withdrawal. A low-dose oral naltrexone challenge has been used as an alternative.

Dosing

''Oral naltrexone'' can be dosed at: 50 mg daily or three times weekly dosing with two 100-mg doses followed by one 150-mg dose. Oral naltrexone seems to be most useful when there is a support person to administer and supervise the medication. A support person may be a family member, close friend, or an employer.

''Extended-release injectable naltrexone'' can be given every 4 weeks by deep intramuscular (IM) injection in the gluteal muscle at a set dosage of 380 mg per injection. Whereas the injection interval is generally every 4 weeks, some clinicians have administered the medication more frequently (eg, every 3 weeks). There is no objective evidence supporting the safety or efficacy of this practice, however, and the Guideline Committee did not endorse it. More research is needed on safe dosing intervals for long-acting injectable naltrexone.

Special consideration should be made in naltrexone dosing for incarcerated groups. Re-entry into the community after imprisonment is a high-risk period for relapse to opioid misuse and overdose. Therefore, extended-release injectable naltrexone dosing before re-entry may serve to prevent relapse and overdose. A similar situation may apply to individuals leaving detoxification with no meaningful follow-up treatment, or to persons who have been detoxified in the course of medical or surgical treatment and who leave the hospital with no immediate relapse prevention follow-up therapy.

Adverse Effects

Naltrexone, both oral and extended-release injectable, is generally well tolerated. Apart from opioids, it does not typically interact with other medications. Most common side effects in random order can include 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. To reduce injection site reactions in obese patients, a longer needle size may be used.[32]

Psychosocial Treatment

Psychosocial treatment is recommended and its efficacy is established when used in combination with naltrexone. Extended-released injectable naltrexone has not been studied as a standalone therapy without psychosocial treatment (for more recommendations regarding psychosocial treatment, see "Part 7: Psychosocial Treatment in Conjunction with Medications for the Treatment of Opioid Use Disorder").

Monitoring Treatment

Patients should be seen frequently at the beginning of their treatment. Weekly or more frequent visits are recommended until patients are determined to be stable. The stability of a patient is determined by an individual clinician based on a number of indicators which may include abstinence from illicit drugs, participation in psychosocial treatment and other recovery-based activities, and good occupational and social functioning. Stable patients can be seen less frequently, but should be seen at least monthly.

Accessing PDMP data is advisable to check for use of other prescription medications. In addition, objective measurement of body fluids for the presence of drugs of misuse is recommended.

Urine drug testing is a reasonably practical and reliable method to test for illicit drugs. However, other reliable biological tests for the presence of drugs may be used. It is recommended that patients be tested often and that testing should be done for substances such as heroin and marijuana, and prescription medications including benzodiazepines, prescription opioids, and amphetamines. How often and exactly what drugs should be tested for to optimize treatment has not been definitively established and is a topic that should be researched further.[16]

Length of Treatment

Data are not available at present on the recommended length of treatment with oral naltrexone or extended-release injectable naltrexone. Duration of treatment depends on the response of the individual patient, the patient's individual circumstances, and clinical judgment.

Switching Treatment Medications

Switching from naltrexone to other opioid treatment medications may be appropriate in the following cases:

(1) Patient experiences intolerable side effects.
(2) Patient has not experienced a successful course of treatment in attaining or maintaining goal through the initially chosen pharmacotherapy option.
(3) Patient wants to change medications and is a candidate for alternative treatment.

Transfer of medications should be planned, considered, and monitored. Switching from an antagonist such as naltrexone to a full agonist (methadone) or a partial agonist (buprenorphine) is generally less complicated than switching from a full or partial agonist to an antagonist because there is no physical dependence associated with antagonist treatment. Patients being switched from naltrexone to buprenorphine or methadone will not have

physical dependence on opioids and thus the initial doses of methadone or buprenorphine used may be less. Patients should not be switched until a significant amount of the naltrexone is no longer in their system – about 1 day for oral naltrexone or 30 days for extended-release injectable naltrexone.

Summary of Recommendations

(1) Naltrexone is a recommended treatment in preventing relapse in opioid use disorder. Oral formula naltrexone may be considered for patients in whom adherence can be supervised or enforced. Extended-release injectable naltrexone may be more suitable for patients who have issues with adherence.
(2) Oral naltrexone should be taken daily in 50-mg doses, or three times weekly in two 100-mg doses followed by one 150-mg dose.
(3) Extended-release injectable naltrexone should be administered every 4 weeks by deep IM injection in the gluteal muscle at a set dosage of 380 mg per injection.
(4) Psychosocial treatment is recommended in conjunction with treatment with naltrexone. The efficacy of naltrexone use in conjunction with psychosocial treatment has been established, whereas the efficacy of extended-release injectable naltrexone without psychosocial intervention "has not" been established.
(5) There is no recommended length of treatment with oral naltrexone or extended-release injectable naltrexone. Duration depends on clinical judgment and the patient's individual circumstances. Because there is no physical dependence associated with naltrexone, it can be stopped abruptly without withdrawal symptoms.
(6) Switching from naltrexone to methadone or buprenorphine should be planned, considered, and monitored. Switching from an antagonist such as naltrexone to a full agonist (methadone) or a partial agonist (buprenorphine) is generally less complicated than switching from a full or partial agonist to an antagonist because there is no physical dependence associated with antagonist treatment and thus no possibility of precipitated withdrawal. Patients being switched from naltrexone to buprenorphine or methadone will not have physical dependence on opioids and thus the initial doses of methadone or buprenorphine used should be low. Patients should not be switched until a significant amount of the naltrexone is no longer in their system – about 1 day for oral naltrexone or 30 days for extended-release injectable naltrexone.
(7) Patients who discontinue antagonist therapy and resume opioid use should be made aware of the increased risks associated with an opioid overdose, and especially the increased risk of death.

Areas for Further Research

(1) Further research is needed to test the relative efficacy of extended-release injectable naltrexone as compared to agonist treatment.
(2) Further research is needed on optimal withdrawal management to initiate treatment with naltrexone and minimize the risk of precipitated withdrawal.

(3) Further research is needed about the safety and efficacy of administering extended-release injectable naltrexone every 3 weeks for individuals who metabolize naltrexone at higher rates.

PART 7: PSYCHOSOCIAL TREATMENT IN CONJUNCTION WITH MEDICATIONS FOR THE TREATMENT OF OPIOID USE DISORDER

Background

Psychosocial treatment can help patients manage cravings, reduce the likelihood of relapse, and assist them in coping with the emotional and social challenges that often accompany substance use disorders. Psychosocial treatment is available in a variety of outpatient and inpatient settings, but the majority of studies have focused on outpatient treatment. Psychosocial treatment is provided using a variety of approaches in various milieus, including social skills training; individual, group, and couples counseling; cognitive behavioral therapy; motivational interviewing; and family therapy. Determining level of need and best approach to psychosocial treatment is individualized to each patient. In accordance with ASAM policy, mutual help compliments professional treatment, but is not a substitute for professional treatment.[92]

Goals of Psychosocial Treatment for Opioid Use Disorder

Although psychosocial treatment options vary, common therapeutic goals are to:

(1) modify the underlying processes that maintain or reinforce use behavior;
(2) encourage engagement with pharmacotherapy (eg, medication compliance); and
(3) treat any concomitant psychiatric disorders that either complicate a substance use disorder or act as a trigger for relapse.

Components of Psychosocial Treatment for Opioid Use Disorder

Psychosocial treatment is recommended in conjunction with any/all pharmacological treatment for opioid use disorder. At a minimum, the psychosocial treatment component of the overall treatment program should include the following:

(1) assessment of psychosocial needs;
(2) supportive individual and/or group counseling;
(3) linkages to existing family support systems; and
(4) referrals to community-based services.

More structured psychosocial treatment may be offered, and may potentially include more intensive individual counseling and psychotherapy, more specific social needs assistance (eg, employment, housing, and legal services), and case management.

Efficacy of Psychosocial Treatments in Opioid Use Disorder

There is evidence of the superiority of some psychosocial treatments over others, particularly contingency management (CM) and cognitive behavioral therapy (CBT). A 2008 meta-analysis compared the 2340 participants who received one of the following interventions: CM, relapse prevention, CBT, and CBT combined with CM. Participants receiving any psychosocial treatment had better outcomes than participants who did not. Contingency management and the combined CM and CBT intervention produced better outcomes than the other interventions.[93]

Other potentially useful psychosocial treatments include, but are not limited to the following:

(1) behavioral couples counseling;
(2) cognitive behavioral coping skills training;
(3) community reinforcement approach;
(4) contingency management/motivational incentives; and
(5) motivational enhancement.

Most recommendations for psychosocial treatments are not correlated with any specific pharmacological approach. Many patients have been shown to experience improved outcomes after receiving psychosocial treatment, in both individual and group formats, from a variety of approaches. Ancillary drug addiction counseling and mutual-help programs are generally considered beneficial.

Mutual Help Programs

Although not considered by ASAM to be a psychosocial treatment on its own, mutual help is an ancillary service that may be effective. Mutual-help programs may include 12-step programs such as Alcoholics Anonymous (AA), Narcotics Anonymous (NA), and Methadone Anonymous (MA). Other mutual-help groups include Self-Management and Recovery Therapy (SMART), and Moderation Management. Many providers recommend mutual-help programs, but there is anecdotal information to suggest that some of these programs may be less acceptable to patients receiving medications for opioid use disorder.

Adherence to Psychosocial Treatment Within Overall Treatment

Clinicians should determine the optimal type of psychosocial treatment to which to refer patients based on shared decision-making with the patient and in consideration of the availability and accessibility of area resources. Collaboration with qualified behavioral health providers is one way for clinicians to determine the type of psychosocial treatment that would best fit within a patient's individualized treatment plan. The ASAM Standards describe in standards III.1 and III.2 the role of the clinician in coordinating care and providing therapeutic alternatives. Key concepts within these standards speak to the importance of patient education about alternatives, shared decision-making in selection of therapeutic services, and the incumbent responsibility of the clinician to assure through the treatment planning and treatment

management processes to assure that psychosocial treatment is being received and that the patient is progressing towards mutually agreed upon goals. Renegotiated treatment plans should be established when patients do not follow through with psychosocial treatment referrals and/or that it is determined that the treatment plan goals are not being advanced.

Psychosocial Treatment and Treatment with Methadone

Psychosocial treatment is generally recommended for patients in treatment with methadone (see "Part 4: Methadone," subsection "Patient Selection and Treatment Goals"). Studies have found that psychosocial treatment in conjunction with methadone pharmacotherapy improves treatment effectiveness. The addition of psychosocial treatment has been associated with improved retention and reduced opioid use. A meta-analysis in 2011 found that psychosocial treatment improved withdrawal management outcomes.[28]

Some research, however, suggests the lack of efficacy in adding psychosocial treatment to treatment with methadone alone. Analyses of specific psychosocial treatments, including contingency management, did not show significant benefit over agonist medication alone.[93] This analysis, however, did not examine the effect of existing psychosocial treatments given during the course of treatment with methadone. Instead, the meta-analysis measured the effect of added psychosocial treatments.

Psychosocial Treatment and Treatment with Buprenorphine

Clinicians who are prescribing buprenorphine should consider providing or recommending office-based or community-based psychosocial treatment. There is some research evidence that the addition of psychosocial treatment improves adherence and retention in treatment with buprenorphine[63,94,95]; however, these findings are mixed.[29,96–99] It is recommended that clinicians offer patients psychosocial treatment early in their treatment with buprenorphine.

Effective therapies may include the following:

(1) cognitive behavioral therapies;
(2) contingency management;
(3) relapse prevention; and
(4) motivational interviewing.

Psychosocial Treatment and Treatment with Naltrexone

Psychosocial treatment is a recommended component of the treatment plan that utilizes the pharmacological therapy of naltrexone. In fact, extended-release injectable naltrexone's efficacy was established only when used in combination with psychosocial treatment. Conversely, extended-release injectable naltrexone's efficacy has not been tested as a standalone treatment without a psychosocial component. There are, however, limited data available on long-term outcomes.

Summary of Recommendations

(1) Psychosocial treatment is recommended in conjunction with any pharmacological treatment of opioid use disorder. At a minimum, psychosocial treatment should include the following: psychosocial needs assessment, supportive counseling, links to existing family supports, and referrals to community services.
(2) Treatment planning should include collaboration with qualified behavioral healthcare providers to determine the optimal type and intensity of psychosocial treatment and for renegotiation of the treatment plan for circumstances in which patients do not adhere to recommended plans for, or referrals to, psychosocial treatment.
(3) Psychosocial treatment is generally recommended for patients who are receiving opioid agonist treatment (methadone or buprenorphine).
(4) Psychosocial treatment should be offered with oral and extended-release injectable naltrexone. The efficacy of extended-release injectable naltrexone to treat opioid use disorder has not been confirmed when it has been used as pharmacotherapy without accompanying psychosocial treatment.

Areas for Further Research

(1) Further research is needed to identify the comparative advantages of specific psychosocial treatments.
(2) Further study is needed to evaluate the effectiveness of psychosocial treatment in combination with specific pharmacotherapies.
(3) More research is needed on which concurrent psychosocial treatments are most effective for different patient populations and treatment settings including primary care.
(4) Further research is needed on which psychosocial treatments are suitable for addition to buprenorphine or treatment with naltrexone, which can be delivered in primary care settings.

PART 8: SPECIAL POPULATIONS: PREGNANT WOMEN

Background

Many of the medical risks associated with opioid use disorder are similar for both pregnant and nonpregnant women; however, opioid use disorder carries obstetrical risks for pregnant women. Several obstetrical complications have been associated with opioid use in pregnancy, including preeclampsia, miscarriage, premature delivery, fetal growth restriction, and fetal death.[100] It is difficult to establish the extent to which these problems are due to opioid use, withdrawal, or co-occurring use of other drugs. Other factors that may contribute to obstetrical complications include concomitant maternal medical, nutritional, and psychosocial issues.

Pregnant women with opioid use disorder are candidates for opioid agonist treatment if a return to opioid use is likely during pregnancy. Methadone is the accepted standard of care for use during pregnancy. Buprenorphine monoproduct is a reasonable and recommended alternative to methadone for pregnant women. There is insufficient evidence to recommend the combination buprenorphine/naloxone formulation, though there is evidence of safety.

Assessment of Opioid Use Disorder in Pregnant Women

As is the case for any patient presenting for assessment of opioid use disorder, the first clinical priority should be to identify any emergent or urgent medical conditions that require immediate attention. Diagnosing emergent conditions can be challenging because women may present with symptoms that may be related to overdose and/or a complication in pregnancy.

A comprehensive assessment including medical examination and psychosocial assessment is recommended in evaluating opioid use disorder in pregnant women. The clinician should ask questions in a direct and nonjudgmental manner to elicit a detailed and accurate history.

Medical Examination

Physical Examination

A physical examination should be conducted for pregnant women who are presenting with potential opioid use disorder. The examination should include identifying objective physical signs of opioid intoxication or withdrawal. The objective physical signs for patients, including pregnant women, are described in "Part 1: Assessment and Diagnosis of Opioid Use Disorder."

Obstetricians and gynecologists should be alert to signs and symptoms of opioid use disorder. Pregnant women with opioid use disorder are more likely to seek prenatal care late in pregnancy, miss appointments, experience poor weight gain, or exhibit signs of withdrawal or intoxication. Positive results of serologic tests for HIV, hepatitis B, or hepatitis C may also indicate opioid use disorder.

On physical examination, some signs of drug use may be present, such as puncture marks from intravenous injection, abscesses, or cellulitis.

Laboratory Tests

Routine prenatal laboratory tests should be performed. Women who use opioids intravenously are at high risk for infections related to sharing injection syringes and sexually transmitted infections. Therefore, counseling and testing for HIV should be provided, according to state laws. Tests for hepatitis B and C and liver function are also suggested. Hepatitis A and B vaccination is recommended for those whose hepatitis serology is negative.

Urine drug testing may be used to detect or confirm suspected opioid and other drug use, but should be performed only with the patient's consent and in compliance with state laws. State laws differ in terms of clinicians' reporting requirements of identified drug use to child welfare services and/or health authorities. Laws that penalize pregnant women for substance use disorders serve to prevent women from obtaining prenatal care and treatment for opioid use disorder, which may worsen outcomes for mother and child. According to the American Congress of Obstetricians and Gynecologists (ACOG) 2014 Toolkit on State Legislation, mandatory urine drug testing is considered an unfavorable policy that does not support healthy pregnancy outcomes.[16] Routine urine drug testing is not highly sensitive for many drugs and results in false-positive and negative results that are misleading and potentially devastating for the patient. ACOG suggests that even with patient consent, urine testing should not be relied upon as the sole or valid indication of drug use. They suggest that positive urine screens should be followed with a definitive drug assay. Similarly, in a study conducted on pregnant women in Florida, where there is mandatory reporting to health authorities, study authors identified that compliant clinician reporting of drug misuse was biased by racial ethnicity and socioeconomic status of the pregnant woman. It was their conclusion that any state that regulates for mandatory urine testing and reporting do so based on medical criteria and medical necessity of such testing.[101]

Imaging

Confirmation of a viable intrauterine pregnancy by sonography is often required before acceptance into an OTP that is tailored specifically to pregnant women. Imaging is also useful for confirmation of gestational age.

Psychosocial Assessment

Research has found that the majority of women entering treatment for opioid use disorder have a history of sexual assault, domestic violence, and/or come from homes where their parents used drugs. Therefore, it is important to obtain a psychosocial history when evaluating pregnant women for opioid use disorder.

Opioid Agonist Treatment in Pregnancy

Decisions to use opioid agonist medications in pregnant women with opioid use disorder revolve around balancing the risks and benefits to maternal and infant health. Opioid agonist treatment is thought to have minimal long-term developmental impacts on children relative to harms resulting from maternal use of heroin and prescription opioids. Therefore, women with opioid use disorder who are not in treatment should be encouraged to start opioid agonist treatment with methadone or buprenorphine monotherapy (without naloxone) as early in the pregnancy as possible. Furthermore, pregnant women who are on agonist treatment should be encouraged not to discontinue treatment while they are pregnant.

Treatment Management Team

Pregnancy in women with opioid use disorder should be co-managed by an obstetrician and an addiction specialist physician. Release of information forms need to be completed to ensure communication among healthcare providers.

Opioid Agonists Versus Withdrawal Management

Pregnant women who are physically dependent on opioids should receive treatment using agonist medications rather than withdrawal management or abstinence as these approaches may pose a risk to the fetus. Furthermore, withdrawal management has been found to be inferior in effectiveness over pharmacotherapy with opioid agonists and increases the risk of relapse without fetal or maternal benefit.

Methadone Versus Buprenorphine

The discussion and decision for medication should be reviewed with the patient and documented in her chart. For

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women who are pregnant or breastfeeding, opioid agonist treatment with methadone or buprenorphine is seen as the most appropriate treatment, taking into consideration effects on the fetus, neonatal abstinence syndrome, and impacts on perinatal care and parenting of young children.

Methadone is the accepted standard of care for use during pregnancy; however, buprenorphine monoproduct is a reasonable alternative and also has some advantages over methadone. Infants born to mothers treated with buprenorphine had shorter hospital stays (10 vs. 17.5 days), had shorter treatment durations for neonatal abstinence syndrome (NAS) (4.1 vs. 9.9 days), and required a lower cumulative dose of morphine (1.1 vs. 10.4 mg) compared to infants born to mothers on treatment with methadone.[102] However, in this trial, mothers treated with buprenorphine were more likely to drop out of treatment compared to mothers treated with methadone.

Combination Buprenorphine/Naloxone

There is some evidence suggesting that buprenorphine/naloxone is equivalent in safety and efficacy to the monoproduct for pregnant women.[103,104] At present, however, this evidence is insufficient to recommend the combination buprenorphine/naloxone formulation in this population. The buprenorphine monoproduct should be used instead.

Naltrexone in Pregnancy

If a woman becomes pregnant while she is receiving naltrexone, it is appropriate to discontinue the medication if the patient and doctor agree that the risk of relapse is low. If the patient is highly concerned about relapse and wishes to remain on naltrexone, it is important to inform the patient about the risks of staying on naltrexone and obtain consent for ongoing treatment. If the patient discontinues treatment with naltrexone and subsequently relapses, it may be appropriate to consider methadone or treatment with buprenorphine.

Naloxone in Pregnancy

The use of an antagonist such as naloxone to diagnose opioid use disorder in pregnant women is contraindicated because induced withdrawal may precipitate preterm labor or fetal distress. Naloxone should be used only in the case of maternal overdose to save the woman's life.

Methadone Induction

Conception While in Treatment with Methadone

Conceiving while on methadone has been associated with better drug treatment outcomes compared to women who initiate methadone during pregnancy. Pregnant women in treatment with methadone before conception who are not in physical withdrawal can be continued on methadone as outpatients.

Timing of Treatment in Pregnancy

Treatment with methadone should be initiated as early as possible during pregnancy to produce the most optimal outcomes. Longer duration of treatment with methadone is associated with longer gestation and higher birth weight.[105]

There is insufficient evidence of teratogenic effects in pregnancy. NAS occurs while under treatment with methadone, but is easily treated if all parties are aware that it is likely to occur. The NAS risk to the fetus is significantly less than the risk of untreated opioid dependence. Data collected on exposure in human pregnancies are complicated by confounding variables including drug, alcohol, and cigarette use; poor maternal nutrition; and an increased prevalence of maternal infection.

The optimum setting for initiation of therapy has not been evaluated in this population. Hospitalization during initiation of treatment with methadone may be advisable due to the potential for adverse events (eg, overdose and adverse drug interactions), especially in the third trimester. This is also an ideal time for the woman to be assessed by a social worker and case manager, and initiate prenatal care if it has not been initiated earlier.

In an inpatient setting, methadone is initiated at a dose range from 10 to 30 mg. Incremental doses of 5–10 mg are given every 3–6 hours as needed to treat withdrawal symptoms, to a maximum first day dose of 30–40 mg. After induction, clinicians should increase the methadone dose in 5–10-mg increments per week, if indicated, to maintain the lowest dose that controls withdrawal symptoms and minimizes the desire to use additional opioids.

Buprenorphine Induction

Initiation or induction of buprenorphine may lead to withdrawal symptoms in patients with physical dependence on opioids. To minimize this risk, induction should be initiated when a woman begins to show objective, observable signs of moderate withdrawal, but before severe withdrawal symptoms are evidenced. This usually occurs 6 hours or more after the last dose of a short-acting opioid, and typically 24–48 hours after the use of long-acting opioids. Hospitalization during initiation of treatment with buprenorphine may be advisable due to the potential for adverse events, especially in the third trimester.

Drug dosing is similar to that in women who are not pregnant (see ''Part 5: Buprenorphine'' for more information).

Dosing of Opioid Agonists During Pregnancy

Methadone Dosing

In the second and third trimester, methadone doses may need to be increased due to increased metabolism and circulating blood volume. With advancing gestational age, plasma levels of methadone progressively decrease and clearance increases.[106–109] The half-life of methadone falls from an average of 22–24 hours in nonpregnant women to 8.1 hours in pregnant women.[110] As a result, ''increased'' or split methadone doses may be needed as pregnancy progresses to maintain therapeutic effects. Splitting the methadone dose into two 12-hour doses may produce more adequate opioid replacement in this period. There is frequent misconception that doses of methadone should decrease as pregnancy progresses; however, data refute this misconception. The risk and severity of NAS are not correlated with methadone doses taken by the mother at the time of delivery and tapering of

dose is not indicated.[111,112] After birth, the dose of methadone may need to be adjusted.

Buprenorphine Dosing

The need to adjust dosing of buprenorphine during pregnancy is less than that of methadone. Clinicians may consider split dosing in patients who complain of discomfort and craving in the afternoon and evening.

Breastfeeding

Mothers receiving methadone and buprenorphine monoproduct for the treatment of opioid use disorders should be encouraged to breastfeed. Naltrexone is not recommended for use during breastfeeding.[82]

Specialty advice should be sought for women with concomitant medical or substance use disorders. Contraindications or precautions in breastfeeding include the following:

(1) HIV-positive mothers.
(2) Mothers using alcohol, cocaine, or amphetamine-type drugs.

Guidelines from the Academy of Breastfeeding Medicine encourage breastfeeding for women treated with methadone who are enrolled in methadone programs.[113] Some of the benefits include improved maternal–infant bonding and favorable effects on NAS.[114,115] It is not clear whether the favorable effects of breastfeeding on NAS are related to the breast milk itself or the act of breastfeeding.[115,116] In a study of buprenorphine and breastfeeding, it was shown that the amount of buprenorphine metabolites secreted in breast milk are so low that they pose little risk to breastfeeding infants.[117]

Summary of Recommendations

(1) The first priority in evaluating pregnant women for opioid use disorder should be to identify emergent or urgent medical conditions that require immediate referral for clinical evaluation.
(2) A medical examination and psychosocial assessment is recommended when evaluating pregnant women for opioid use disorder.
(3) Obstetricians and gynecologists should be alert to signs and symptoms of opioid use disorder. Pregnant women with opioid use disorder are more likely to seek prenatal care late in pregnancy, miss appointments, experience poor weight gain, or exhibit signs of withdrawal or intoxication.
(4) Psychosocial treatment is recommended in the treatment of pregnant women with opioid use disorder.
(5) Counseling and testing for HIV should be provided in accordance with state law. Tests for hepatitis B and C and liver function are also suggested. Hepatitis A and B vaccination is recommended for those whose hepatitis serology is negative.
(6) Urine drug testing may be used to detect or confirm suspected opioid and other drug use with informed consent from the mother, realizing that there may be adverse legal and social consequences of her use. State laws differ on reporting substance use during pregnancy.

Laws that penalize women for use and for obtaining treatment serve to prevent women from obtaining prenatal care and worsen outcomes.

(7) Pregnant women who are physically dependent on opioids should receive treatment using methadone or buprenorphine monoproduct rather than withdrawal management or abstinence.
(8) Care for pregnant women with opioid use disorder should be comanaged by an obstetrician and an addiction specialist physician. Release of information forms need to be completed to ensure communication among healthcare providers.
(9) Treatment with methadone should be initiated as early as possible during pregnancy.
(10) Hospitalization during initiation of methadone and treatment with buprenorphine may be advisable due to the potential for adverse events, especially in the third trimester.
(11) In an inpatient setting, methadone should be initiated at a dose range of 20–30 mg. Incremental doses of 5–10 mg are given every 3–6 hours, as needed, to treat withdrawal symptoms.
(12) After induction, clinicians should increase the methadone dose in 5–10-mg increments per week. The goal is to maintain the lowest dose that controls withdrawal symptoms and minimizes the desire to use additional opioids.
(13) Twice-daily dosing is more effective and has fewer side effects than single dosing, but may not be practical because methadone is typically dispensed in an outpatient clinic.
(14) Clinicians should be aware that the pharmacokinetics of methadone are affected by pregnancy. With advancing gestational age, plasma levels of methadone progressively decrease and clearance increases. Increased or split doses may be needed as pregnancy progresses. After child birth, doses may need to be adjusted.
(15) Buprenorphine monoproduct is a reasonable and recommended alternative to methadone for pregnant women. Whereas there is evidence of safety, there is insufficient evidence to recommend the combination buprenorphine/naloxone formulation.
(16) If a woman becomes pregnant while she is receiving naltrexone, it is appropriate to discontinue the medication if the patient and doctor agree that the risk of relapse is low. If the patient is highly concerned about relapse and wishes to continue naltrexone, she should be informed about the risks of staying on naltrexone and provide her consent for ongoing treatment. If the patient wishes to discontinue naltrexone, but then reports relapse to opioid use, it may be appropriate to consider treatment with methadone or treatment with buprenorphine.
(17) Naloxone is not recommended for use in pregnant women with opioid use disorder except in situations of life-threatening overdose.
(18) Mothers receiving methadone and buprenorphine monoproduct for the treatment of opioid use disorders should be encouraged to breastfeed.

Areas for Further Research

Further research is needed to establish the safety of buprenorphine or the combination of the buprenorphine/naloxone for use in pregnancy.

PART 9: SPECIAL POPULATIONS: INDIVIDUALS WITH PAIN

Background

The occurrence of acute and chronic pain among patients with an opioid use disorder is not uncommon. Because of the current epidemic of nonmedical prescription drug use, it is critical to know how to manage pain safely and effectively. There are three general situations (listed below), each of which will be addressed separately, in which patients with opioid use disorder could be treated for pain:

(1) Pain in patients with an untreated and active opioid use disorder
(2) Pain in patients under opioid use disorder treatment with opioid agonists
(3) Pain in patients under opioid use disorder treatment with naltrexone

General Considerations for All Patients With Pain

For all patients with pain, it is important that the correct diagnosis of pain etiology be made and that a suitable treatment be identified. Nonpharmacological treatments have been shown to be effective for pain (eg, physical therapy) and may be considered.

If pharmacological treatment is considered, then non-narcotic medications such as acetaminophen and NSAIDs should be tried first. Adjunctive medications including anticonvulsants may be useful. Tricyclic antidepressants or combined norepinephrine-serotonin reuptake inhibitors may also be used.

Pain Management in Patients Using Opioids

Opioid agonists (methadone or buprenorphine) may be considered for patients with an active opioid use disorder who are not undergoing treatment. Both methadone and buprenorphine have analgesic effects. Transition to opioid agonist treatments can help co-manage pain and opioid use disorder.

Methadone and Pain Management

Patients prescribed methadone for opioid use disorder treatment should receive pain management in the same way as other patients in consultation with a pain specialist.

Acute and Chronic Pain Control

Because of the tolerance associated with daily methadone dosing, the usual dose of methadone may be inadequate for pain control. Patients in treatment with methadone will require doses of opioids in addition to their regular daily dose of methadone to manage acute pain.[118] However, in some cases, the tolerance associated with daily methadone dosing may result in the need for higher doses of narcotic analgesics.[119,120] Methadone patients who have chronic pain should optimally be treated in consultation with a pain specialist.

Buprenorphine and Pain Management

Acute Pain Control

Although it is a mu-opioid partial agonist, buprenorphine does have analgesic properties. Temporarily increasing buprenorphine dosing or dividing the dose may be effective for acute pain management.

Patients' pain may not be adequately addressed with buprenorphine and may require a full agonist. In situations when a full opioid agonist is needed for pain control, patients may be taken off buprenorphine and switched to a full opioid agonist until analgesia is no longer necessary. This may occur when patients undergo elective surgery. However, there are data to suggest that the discontinuation of buprenorphine is unnecessary and that adequate analgesia may be possible by simply adding non-narcotic and narcotic analgesics to the patient's baseline buprenorphine dose.[121]

For severe acute pain, discontinuing buprenorphine is advisable, and then commencing a high-potency opioid (such as fentanyl) in an attempt to over-ride the partial mu-receptor blockade of the buprenorphine is recommended. Patients should be monitored closely because high doses of a full agonist may be required. As the buprenorphine's partial blockade dissipates, the full agonist effect may lead to over-sedation and respiratory depression. Additional interventions such as regional anesthesia should also be considered.

Chronic Pain Control

Buprenorphine may be adequate for chronic pain control in many patients with opioid use disorder and other types of chronic pain. Chronic opioid therapy, especially at high doses, may heighten pain sensitivity.[122] There is some evidence suggesting that patients experiencing significant pain on high doses of full agonist opioid pain relievers experience improved pain control when transitioned to buprenorphine.[123] Split dosing of buprenorphine should be considered for patients with pain.

Considerations for Buprenorphine in Surgery

Discontinuation of buprenorphine is not recommended before elective cesarean section as it creates the potential for fetal withdrawal. For other elective surgeries in which buprenorphine is discontinued, the last dose of buprenorphine is usually delivered 24–36 hours before the anticipated need for analgesia. The buprenorphine is then restarted after a period of time after the discontinuation of full opioid agonists. Short-acting opioids should be given during or after surgery and titrated to maintain proper analgesia. In cases in which the buprenorphine cannot be stopped abruptly, pain control may be achieved with full opioid agonists added to the buprenorphine, but the doses may need to be increased to overcome the receptor blockade produced by buprenorphine.[124–126] The decision to discontinue buprenorphine before an elective

Naltrexone and Pain Management

Patients on naltrexone will not respond to opioid analgesics in the usual manner. Mild pain may be treated with NSAIDs. Ketorolac may be prescribed for moderate to severe pain, but its use should be time-limited due to higher risk of gastritis.

Emergency pain control options in patients taking naltrexone include the following:

(1) regional anesthesia;
(2) conscious sedation with benzodiazepines or ketamine; and
(3) nonopioid options in general anesthesia.

Considerations for Naltrexone in Surgery

Oral naltrexone should be discontinued at least 72 hours before elective surgery if pain management using opioids is anticipated. Extended-release naltrexone should be stopped at least 30 days before surgery, and oral naltrexone may be used temporarily. The surgical team should be aware of the use of naltrexone. Patients should be off opioids for 3–7 days before resuming naltrexone (oral or extended-release formulations). A naloxone challenge may be used to confirm that opioids are no longer being used.

Summary of Recommendations

(1) For all patients with pain, it is important that the correct diagnosis be made and that a target suitable for treatment is identified.
(2) If pharmacological treatment is considered, non-narcotic medications such as acetaminophen and NSAIDs should be tried first.
(3) Opioid agonists (methadone or buprenorphine) should be considered for patients with active opioid use disorder who are not under treatment.
(4) Pharmacotherapy in conjunction with psychosocial treatment should be considered for patients with pain who have opioid use disorder.
(5) Patients on methadone for the treatment of opioid use disorder will require doses of opioids in addition to their regular daily dose of methadone to manage acute pain.
(6) Patients on methadone for the treatment of opioid use disorder and who are admitted for surgery may require additional short-acting opioid pain relievers. The dose of pain relievers prescribed may be higher due to tolerance.
(7) Temporarily increasing buprenorphine dosing may be effective for mild acute pain.
(8) For severe acute pain, discontinuing buprenorphine and commencing on a high-potency opioid (such as fentanyl) is advisable. Patients should be monitored closely and additional interventions such as regional anesthesia should also be considered.
(9) The decision to discontinue buprenorphine before an elective surgery should be made in consultation with the attending surgeon and anesthesiologist. If it is decided

that buprenorphine should be discontinued before surgery, this should occur 24–36 hours in advance of surgery and restarted postoperatively when the need for full opioid agonist analgesia has passed.
(10) Patients on naltrexone will not respond to opioid analgesics in the usual manner. Therefore, it is recommended that mild pain be treated with NSAIDs and moderate to severe pain be treated with ketorolac on a short-term basis.
(11) Oral naltrexone should be discontinued 72 hours before surgery and extended-release injectable naltrexone should be discontinued 30 days before an anticipated surgery.

Areas for Further Research

Further research is needed to examine whether the discontinuation of buprenorphine before elective surgery is necessary. Studies on whether it is possible to provide adequate analgesia by adding full agonist opioid analgesics to the patient's baseline buprenorphine dose are needed.

PART 10: SPECIAL POPULATIONS: ADOLESCENTS

Background

The American Academy of Pediatrics categorizes adolescence as the totality of three developmental stages – puberty to adulthood – which occur generally between 11 and 21 years of age.[11] Young people within this age group – adolescents – present for treatment with a broad spectrum of opioid use disorder severity and with co-occurring medical and psychiatric illness. Consequently, physicians will need to respond with a full range of treatment options, including pharmacotherapy. However, limited evidence exists regarding the efficacy of opioid withdrawal management in adolescents.[127] Pharmacological therapies have primarily been developed through research with adult populations.[128]

The treatment of adolescents with opioid use disorder presents many unique medical, legal, and ethical dilemmas that may complicate treatment. Given these unique issues, adolescents with opioid use disorder often benefit from services designed specifically for them. Furthermore, the family should be involved in treatment whenever possible.

Confidentiality in Treatment

One issue that may be of particular importance to consider in the treatment of adolescents is confidentiality. Adolescents have reported that they are less likely to seek substance use disorder treatment if services are not confidential.[129] Confidential care, particularly with respect to sensitive issues such as reproductive health and substance use, has become a well established practice.[130,131] This is a subject of complexity as it is an area governed by both Federal and state laws. Moreover, defined age ranges of ''adolescence'' vary. A myriad of clinical and legal responsibilities may be evoked if confronted by a young person's request for confidentiality. More than half of the states in the United States, by law, permit adolescents less than 18 years of age to consent to substance use disorder treatment without parental consent. State law should also be consulted. An additional reference

source in decision-making regarding the implications on coordination of care, effectiveness of treatment without parental communication, and more are fully discussed in a publication of the Substance Abuse and Mental Health Services Administrations (SAMHSA), Center for Substance Abuse Treatment, Treatment Improvement Protocol (TIP) #33.[132]

Pharmacotherapy Options for Adolescents

Opioid agonists (methadone and buprenorphine) and antagonists (naltrexone) may be considered for treatment of opioid use disorder in adolescents. However, efficacy studies for these medications have largely been conducted in adults. This recommendation is based on the consensus opinion of the Guideline Committee. There are virtually no data comparing the relative effectiveness of these treatments in adolescents.

Opioid Agonists: Methadone and Buprenorphine

Agonist medications are indicated for the treatment of patients who are aged 18 years and older. The Federal code on opioid treatment – 42 CFR § 8.12 – offers an exception for patients aged 16 and 17, who have a documented history of at least two prior unsuccessful withdrawal management attempts, and have parental consent.[133]

Efficacy Research on Agonists and Partial Agonists in Adolescents

There are no controlled trials evaluating methadone for the treatment of opioid use disorder in adolescents under the age of 18. Descriptive trials support the usefulness of treatment with methadone in supporting treatment retention in adolescent heroin users.[134] The usefulness of treatment with buprenorphine has been demonstrated in two RCTs. Studies have, however, not included adolescents under the age of 16.[135,136] Buprenorphine is not US FDA-approved for use in patients less than 16 years old. Buprenorphine is more likely to be available in programs targeting older adolescents and young adults. No direct comparison of the efficacy of buprenorphine versus methadone has been conducted in adolescent populations.

Opioid Antagonist: Naltrexone

Naltrexone may be considered for young adults aged 18 years and older who have opioid use disorder. Naltrexone does not induce physical dependence and is easier to discontinue. Oral naltrexone may be particularly useful for adolescents who report a shorter duration of opioid use. Extended-release injectable naltrexone is administered monthly and can be delivered on an outpatient basis. There is only one small case series that demonstrated the efficacy of extended-release injectable naltrexone in adolescents.[137] The safety, efficacy, and pharmacokinetics of extended-release injectable naltrexone have not been established in the adolescent population.

Psychosocial Treatment for Adolescents

Psychosocial treatment is recommended in the treatment of adolescents with opioid use disorder. Recommended treatments based on the consensus opinion of the Guideline Committee include family intervention approaches, vocational support, and behavioral interventions to incrementally reduce use. Holistic risk-reduction interventions, which promote practices to reduce

infection, are particularly important in the prevention of sexually transmitted infections and blood-borne viruses. Treatment of concomitant psychiatric conditions is also especially important in this population. Adolescents often benefit from specialized treatment facilities that provide multiple services.

Summary of Recommendations

(1) Clinicians should consider treating adolescents who have opioid use disorder using the full range of treatment options, including pharmacotherapy.
(2) Opioid agonists (methadone and buprenorphine) and antagonists (naltrexone) may be considered for treatment of opioid use disorder in adolescents. Age is a consideration in treatment, and Federal laws and US FDA approvals need to be considered for patients under age 18.
(3) Psychosocial treatment is recommended in the treatment of adolescents with opioid use disorder.
(4) Concurrent practices to reduce infection (eg, sexual risk-reduction interventions) are recommended as components of comprehensive treatment for the prevention of sexually transmitted infections and blood-borne viruses.
(5) Adolescents may benefit from treatment in specialized treatment facilities that provide multidimensional services.

Areas for Further Research

(1) More studies are needed to examine the efficacy of pharmacotherapy for adolescents with opioid use disorder. Due to the few clinical trials in adolescents, most of the current recommendations are based on research with adults.
(2) More research is needed to identify which psychosocial treatments, alone and in combination with pharmacotherapy, are best suited for use with adolescents.

PART 11: SPECIAL POPULATIONS: INDIVIDUALS WITH CO-OCCURRING PSYCHIATRIC DISORDERS

Background

Co-occurring psychiatric disorders are common among individuals who have opioid use disorder. Epidemiological studies have demonstrated a higher prevalence of substance use among people with psychiatric disorders relative to the general population.[138]

Reasons for the association between psychiatric and substance use disorders are not known. One hypothesis is that the dual diagnoses result from risk factors that are common to both disorders. A shared genetic vulnerability has been proposed to explain dysregulation in dopamine and glutamate systems in schizophrenia and substance use disorders.[139,140] Another hypothesis is that people with psychiatric disorders are more likely to use drugs as a method of self-medication.[141–143]

Co-occurring psychiatric disorders should not bar patients from opioid use disorder treatment. The presence of the following common psychiatric disorders should be evaluated in patients presenting with possible opioid use disorder:

(1) Depression
(2) Anxiety

(3) Personality disorders
(4) Post-traumatic stress disorder.

Assessment of Psychiatric Co-occurrence

The assessment of psychiatric disorders is critical when attempting to place patients in the appropriate treatment. Hospitalization may be appropriate for patients with severe or unstable psychiatric symptoms that may compromise the safety of self and others. An initial patient assessment should determine whether the patient is stable. Patients with suicidal or homicidal ideation should be referred immediately for treatment and possibly hospitalization. Patients should also be assessed for signs or symptoms of acute psychosis and chronic psychiatric disorders.

An assessment including medical history, physical examination, and an assessment of mental health status and/or psychiatric disorder should occur at the beginning of agonist or antagonist treatment (see ''Part 1: Assessment and Diagnosis of Opioid Use Disorder''). Reassessment using a detailed mental status examination should occur after stabilization with methadone, buprenorphine, or naltrexone.

Co-occurring Psychiatric Disorders and Suicide Risk

Psychiatric disorders are strongly associated with suicide. More than 90% of patients who attempt suicide have a major psychiatric disorder.[144] In cases where suicide attempts resulted in death, 95% of patients had a psychiatric diagnosis.[145]

Management of a suicidal patient should include the following:

(1) Reduce immediate risk
(2) Manage underlying factors associated with suicidal intent
(3) Monitor and follow-up

Considerations with Specific Psychiatric Disorders

Depression or Bipolar Disorder

Antidepressant therapy may be initiated with pharmacotherapy for opioid use disorder for patients with symptoms of depression. Patients presenting with mania should be evaluated to determine whether symptoms arise from the bipolar disorder or substance use. Patients with bipolar disorder may require additional psychiatric care, hospitalization, and/or treatment with prescription mood stabilizers.

All patients with depression, including bipolar disorder, should be asked about suicidal ideation and behavior. Patients with a history of suicidal ideation or attempts should have their medication use monitored regularly. This includes medications for the treatment of opioid use disorder and psychiatric medications.

Schizophrenia

Antipsychotic therapy may be initiated with pharmacotherapy for opioid use disorder for patients with schizophrenia or other psychotic disorder. Coadministration of antipsychotic medications with agonist pharmacotherapy or use of long-acting depot formulations of antipsychotic medications is an option to consider in patients with histories of medication nonadherence.

All patients with schizophrenia should be asked about suicidal ideation and behavior. Patients with a history of suicidal ideation or attempts should have their medication use monitored regularly. This includes medications for the treatment of opioid use disorder and psychiatric medications.

For patients with schizophrenia and concomitant opioid use disorder who have a recent history of, or are at risk of repeated hospitalization or homelessness, assertive community treatment (ACT) should be considered. ACT is designed to provide treatment, rehabilitation, and support services to individuals who are diagnosed with severe psychiatric disorders, and whose needs have not been well met by more traditional psychiatric or psychosocial services. The efficacy of ACT has had mixed results on substance use disorder outcomes, but has shown benefit in preventing homelessness.[146–148] When ACT or another intensive case management program is unavailable, traditional case management can be helpful to patients who are unable to manage necessary, basic tasks.

Co-occurring Psychiatric Disorders and Agonist Treatment

Pharmacological and conjunctive psychosocial treatments should be considered for patients with both an opioid use disorder and a psychiatric disorder. Actively suicidal patients are not good candidates for any opioid treatment.

Methadone

Methadone for the treatment of opioid use disorder has been found to reduce psychiatric distress in a few weeks. Psychotherapy has been found useful in patients who have moderate to severe psychiatric disorders.

Buprenorphine

Psychiatrically stable patients are good candidates for buprenorphine. Patients with depression who are receiving treatment with buprenorphine require a higher level of monitoring.

Co-occurring Psychiatric Disorders and Antagonist Treatment

Psychiatrically stable patients are good candidates for treatment with oral naltrexone or extended-release injectable naltrexone. There are little data, however, regarding the relative efficacy of these medications in opioid-dependent patients with co-occurring psychiatric disorders. The once-monthly injections of extended-release injectable naltrexone may be especially useful in patients with a co-occurring psychiatric disorder, who may not be able to adhere well to daily dosing. Patients should be closely observed for adverse events as some patients have reported suicidal ideation, suicide attempts, and depression.

Summary of Recommendations

(1) A comprehensive assessment including determination of mental health status should evaluate whether the patient is

stable. Patients with suicidal or homicidal ideation should be referred immediately for treatment and possibly hospitalization.

(2) Management of patients at risk for suicide should include the following: reducing immediate risk; managing underlying factors associated with suicidal intent; and monitoring and follow-up.

(3) All patients with psychiatric disorders should be asked about suicidal ideation and behavior. Patients with a history of suicidal ideation or attempts should have opioid use disorder, and psychiatric medication use, monitored.

(4) Assessment for psychiatric disorder should occur at the onset of agonist or antagonist treatment. Reassessment using a detailed mental status examination should occur after stabilization with methadone, buprenorphine, or naltrexone.

(5) Pharmacotherapy in conjunction with psychosocial treatment should be considered for patients with opioid use disorder and a co-occurring psychiatric disorder.

(6) Clinicians should be aware of potential interactions between medications used to treat co-occurring psychiatric disorders and opioid use disorder.

(7) Assertive community treatment should be considered for patients with co-occurring schizophrenia and opioid use disorder, who have a recent history of, or are at risk of, repeated hospitalization or homelessness.

PART 12: SPECIAL POPULATIONS: INDIVIDUALS IN THE CRIMINAL JUSTICE SYSTEM

Background

A substantial proportion of persons in prisons, jails, drug courts, probation, parole, and who are criminally involved have opioid use disorder and related problems. A lifetime history of incarceration is common among intravenous drug users; 56–90% of intravenous drug users have been incarcerated previously.[149] The United States leads the world in the number of people incarcerated in Federal and state correctional facilities. There are, at present, more than 2 million people in American prisons. Approximately one-quarter of those people held in US prisons have been convicted of a drug offense.[150] Continued drug use is common among prisoners, and many individuals initiate intravenous drug use while in prison.[151,152]

Prison drug use is particularly risky because of the environment. The high concentration of at-risk individuals and general overcrowding can increase the risk of adverse consequences associated with drug use, including violence, drug-related deaths, suicide, and self-harm.[153] Drugs and sterile injection equipment is rare and sharing needles is common, leading to a high risk of spreading HIV and hepatitis C. Discharge from prison is often associated with opioid overdose and death. Consequently, it is important to identify and implement effective treatments for prisoners and probationers/parolees.

For the purposes of this *Practice Guideline*, a prison is to be differentiated from a jail. At the most basic level, the fundamental difference between jail and prison is the length of stay for inmates. Jails are usually run by local law enforcement and/or local government agencies, and are designed to

hold inmates awaiting trial or serving a short sentence. Prison terms are of longer duration. Anyone incarcerated, regardless of sentence term, should be continued on opioid treatment.

Effectiveness of Pharmacotherapy

Pharmacotherapy for the treatment of opioid use disorder among prisoners has been shown to be effective. Most evidence for the effectiveness of pharmacotherapy for the treatment of opioid use disorder among prisoners has been derived from treatment with methadone. However, there is some evidence supporting the use of buprenorphine and naltrexone in this population.[154]

Methadone

Treatment with methadone has been shown to have a number of beneficial effects in inmates with opioid use disorders. Prisoners with opioid use disorder treated with methadone inject a lesser amount of drugs.[151,155–157] Prisoners treated with methadone used less drugs after release and were more likely to participate in community-based addiction treatment.[158] Treatment with methadone lowered the rate of reincarceration during the 3-year period following first incarceration.[158,159]

Buprenorphine

Although less extensively studied, in some early trials, buprenorphine has also been associated with beneficial effects in prisoners with opioid use disorder. A RCT comparing buprenorphine and methadone among male heroin users who were newly admitted to prison showed that treatment completion rates were similar, but that buprenorphine patients were significantly more likely to enter community-based treatment after release.[160] In a more recent trial, buprenorphine initiated in prison was also associated with a greater likelihood of entering community treatment.[161] However, buprenorphine was diverted in some cases. Although promising, more research needs to be done to establish the effectiveness of inprison treatment with buprenorphine.

Naltrexone

Extended-release injectable naltrexone is the newest, and consequently least studied, medication for the treatment of prisoners and parolees. It has been shown to be effective for the treatment of opioid dependence in some early trials; however, there are no published studies evaluating the effectiveness of extended-release injectable naltrexone for the treatment of opioid use disorder in prisoners. In one small pilot trial involving parolees with prior opioid use disorder, 6 months of treatment with extended-release injectable naltrexone was associated with fewer opioid-positive urine drug screens and a reduced likelihood of reincarceration.[162] There are no studies establishing effectiveness of extended-release injectable naltrexone for persons in prison, or comparing it to either methadone or buprenorphine. Further research is needed in this area.

Treatment Options

All adjudicated individuals, regardless of type of offense and disposition, should be screened for opioid use

disorder and considered for initiation or continuation of medication for the treatment of opioid use disorder. For incarcerated individuals, it should be initiated a minimum of 30 days before release, and aftercare should be arranged in advance.[163]

Methadone and Buprenorphine

Methadone or treatment with buprenorphine that is initiated during incarceration and to be continued after release is recommended for inmates with opioid use disorder without contraindications to these two medications. There is limited research comparing methadone and buprenorphine. In one trial, outcomes after release were similar; however, there was a problem with diversion of buprenorphine.[160]

Naltrexone

Extended-release injectable naltrexone may be considered for prisoners with opioid use disorder. However, there are little data about efficacy in prison populations. Extended-release injectable naltrexone should be considered for patients with opioid use disorder, with no contraindications, before their release from prison. Whether or not extended-release injectable naltrexone is superior to buprenorphine or methadone for the treatment of prisoners with opioid use disorder is unknown.

Summary of Recommendations

(1) Pharmacotherapy for the continued treatment of opioid use disorders, or the initiation of pharmacotherapy, has been shown to be effective and is recommended for prisoners and parolees regardless of the length of their sentenced term.

(2) Individuals with opioid use disorder who are within the criminal justice system should be treated with some type of pharmacotherapy in addition to psychosocial treatment.

(3) Opioid agonists (methadone and buprenorphine) and antagonists (naltrexone) may be considered for treatment. There is insufficient evidence to recommend any one treatment as superior to another for prisoners or parolees.

(4) Pharmacotherapy should be initiated a minimum of 30 days before release from prison.

Areas for Further Research

Further research is needed on the effectiveness of pharmacotherapy in prisoner populations.

PART 13: NALOXONE FOR THE TREATMENT OF OPIOID OVERDOSE

Introduction

Death from opioid overdose is a growing epidemic in the United States. Poisoning deaths involving opioid analgesics have more than tripled in the United States since 1999.[164] Unintentional poisoning (primarily due to drug overdose) is now the leading cause of injury-related death among Americans aged 25–64, having surpassed motor vehicle accidents in 2009.[165] Patients who overdose on opioids are in a life-threatening situation that requires immediate medical intervention. Naloxone is a mu-opioid antagonist with well established safety and efficacy that can reverse opioid overdose and prevent fatalities. As well, naloxone can and should be administered to pregnant women in cases of overdose to save the mother's life.

As of December 15, 2104, a total of 27 states (NM, NY, IL, WA, CA, RI, CT, MA, NC, OR, CO, VA, KY, MD, VT, NJ, OK, UT, TN, ME, GA, WI, MN, OH, DE, PA, and MI) and the District of Columbia amended their state laws to make it easier for medical professionals to prescribe and dispense naloxone, and for lay administrators to use it without fear of legal repercussions.[166] State laws generally dictate various levels of prescriptive authority and generally speaking discourage the prescription of drugs to an individual other than the intended recipient, third-party prescription, or to a person the physician has not examined to be used in specific scenarios to assist others (prescription via standing order).

Patients and Significant Others/Family Members

Patients who are being treated for opioid use disorder, and their family members or significant others, should be given prescriptions for naloxone. Patients and family members/significant others should be trained in the use of naloxone in overdose. The practice of coprescribing naloxone for home use in the event of an overdose situation experienced by the patient or by any others in the household is endorsed by ASAM in a public policy statement and by SAMHSA in its toolkit on opioid overdose.[167,168]

Individuals Trained and Authorized to Use Naloxone

Until recently, administration of naloxone for the treatment of opioid overdose was only recommended for hospital personnel and paramedics. However, efforts are underway to expand the use of naloxone for the treatment of overdose to other first responders, including emergency medical technicians, police officers, firefighters, correctional officers, and others who might witness opioid overdose such as addicted individuals and their families. The primary issues to be considered in this *Practice Guideline* include the safety and efficacy of naloxone for the treatment of opioid overdose by first responders and bystanders, and the best form of naloxone to use for this purpose.

Safety and Efficacy of Bystander Administered Naloxone

Although there is ample evidence supporting the safety and efficacy of naloxone for the treatment of opioid overdose,[164,169,170] less is known about the effectiveness of naloxone used by other first responders and bystanders. Naloxone has been shown to be effective when used by paramedics.[171,172] There are no trials specifically evaluating the effectiveness of naloxone when administered by nonmedical first responders such as police officers and firefighters.

There have been a number of nonrandomized studies evaluating the effectiveness of community-based overdose prevention programs that include the distribution of naloxone

to nonmedical personnel. In a comprehensive review of these trials, Clark et al.[164] concluded that bystanders (mostly opioid users) can and will use naloxone to reverse opioid overdose when properly trained, and that this training can be done successfully through these programs. The authors acknowledge that the lack of randomized controlled trials of community-based overdose prevention programs limits conclusions about their overall effectiveness. SAMHSA supports the use of naloxone for the treatment of opioid overdose by bystanders in their Opioid Overdose Prevention Toolkit.[168]

Routes of Administration

Naloxone is marketed in vials for injection and in an autoinjector for either IM or subcutaneous (SC) use. The US FDA-approved autoinjectors were designed to be used by a patient or family member for the treatment of opioid overdose. There is not yet an US FDA-approved intranasal formulation – there are only kits made available to deliver the injectable formulation intranasally. Despite the intranasal formulation's current lack of US FDA approval, it is being used off-label by first responders.

Although there are some data from head-to-head trials suggesting that IM naloxone may be superior to intranasal naloxone, there are few studies comparing the superiority of naloxone by route of administration, including intranasal, IM, or intravenous. The present available intranasal naloxone formulation is not dispensed in a preloaded syringe and this may affect its usefulness.[173] More research is needed to definitively assess the relative effectiveness of injectable vs. intranasal naloxone. In addition, the development of a more convenient administration device for intranasal naloxone could improve the effectiveness of this form of naloxone.

Summary of Recommendations

(1) Naloxone should be given in case of opioid overdose.
(2) Naloxone can and should be administered to pregnant women in cases of overdose to save the mother's life.
(3) The Guideline Committee, based on consensus opinion, recommends that patients who are being treated for opioid use disorder and their family members/significant others be given prescriptions for naloxone. Patients and family members/significant others should be trained in the use of naloxone in overdose.
(4) The Guideline Committee, based on consensus opinion, recommends that first responders, for example, emergency medical services personnel, police officers, and firefighters be trained in and authorized to administer naloxone.

PART 14: AREAS FOR FURTHER RESEARCH

Although this *Practice Guideline* is intended to guide the assessment, treatment, and use of medications in opioid use disorder, there are areas where there was insufficient evidence to make a recommendation. Further research is needed to compare the advantages of different medications for different patient groups, especially with the emergence of new treatments. The recommended areas of future research are outlined below and presented in the order they were introduced in the guideline.

Assessment and Diagnosis of Opioid Use Disorder (Part 1)

(1) More research is needed on best practices for drug testing during the initial evaluation and throughout the entire treatment process.
(2) Further research is needed on evidence-based approaches for treating opioid use disorder in patients who continue to use marijuana and/or other psychoactive substances.
(3) Whereas research indicates that offering tobacco cessation is a standard for all medical care, more research is needed before specific evidence-based recommendations can be made.

Treatment Options (Part 2)

(1) More research is needed to compare the advantages of agonists and antagonists in the treatment of opioid use disorder. Whereas methadone, buprenorphine, and naltrexone are all superior to no treatment in opioid use disorder, less is known about their relative advantages.

Opioid Withdrawal Management (Part 3)

(1) Further research is needed to evaluate the efficacy and safety of alpha-2 adrenergic and other nonopioid medications that are being used off-label for withdrawal management. These nonopioid medications may have use in transitioning patients onto antagonists for relapse prevention.
(2) Further study is needed on other methods to accelerate the withdrawal process and facilitate the introduction of antagonists.
(3) More research is needed to make recommendations on the optimal duration of a buprenorphine taper.
(4) More research is needed to evaluate the safety of inpatient as compared to outpatient withdrawal management.
(5) More research is needed to compare the effectiveness of short versus long tapers with buprenorphine withdrawal management.

Methadone (Part 4)

(1) Further research is needed to assess the effectiveness of added psychosocial treatment to treatment with methadone in OTP or inpatient settings. Treatment with methadone generally includes some psychosocial components. However, it is unclear whether added psychosocial treatment improves patient outcomes.

Research is needed to evaluate the use of ECG in treatment with methadone in preventing adverse events.

Buprenorphine (Part 5)

(1) Further research is needed to evaluate the safety and efficacy of buprenorphine induction conducted in the patient's own home, although present research supports this practice in select cases.

Naltrexone (Part 6)

(1) Further research is needed to test the relative efficacy of extended-release injectable naltrexone as compared to agonist treatment.

(2) Further research is needed on optimal withdrawal management to initiate treatment with naltrexone and minimize the risk of precipitated withdrawal.

(3) Further research is needed about the safety and efficacy of administering extended-release injectable naltrexone every 3 weeks for individuals who metabolize naltrexone at higher rates.

Psychosocial Treatment in Conjunction With Medications for the Treatment of Opioid Use Disorder (Part 7)

(1) Further research is needed to identify the comparative advantages of specific psychosocial treatments.

(2) Further study is needed to evaluate the effectiveness of psychosocial treatment in combination with specific pharmacotherapies.

(3) More research is needed on which concurrent psychosocial treatments are most effective for different patient populations and treatment settings including primary care.

(4) Further research is needed on which psychosocial treatments are suitable for addition to buprenorphine or treatment with naltrexone, which can be delivered in primary care settings.

Special Populations: Pregnant Women (Part 8)

(1) Further research is needed to establish the safety of buprenorphine or the combination of the buprenorphine/naloxone for use in pregnancy.

Special Population: Individuals With Pain (Part 9)

(1) Further research is needed to examine whether the discontinuation of buprenorphine before elective surgery is necessary. Studies on whether it is possible to provide adequate analgesia by adding full agonist opioid analgesics to the patient's baseline buprenorphine dose are needed.

Special Populations: Adolescents (Part 10)

(1) More studies are needed to examine the efficacy of pharmacotherapy for adolescents with opioid use disorder. Due to the few clinical trials in adolescents, most of the present recommendations are based on research with adults.

(2) More research is needed to identify which psychosocial treatments, alone and in combination with pharmacotherapy, are best suited for use with adolescents.

Special Populations: Individuals in the Criminal Justice System (Part 12)

(1) Further research is needed on the effectiveness of pharmacotherapy in prisoner populations.

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5.. Washington, D.C.: American Psychiatric Association; 2013.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV. Washington, D.C.: American Psychiatric Association; 1994.
3. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization; 1992.
4. Mee-Lee D, Shulman GD, Fishman MJ, et al., eds. The ASAM Criteria: Treatment Criteria for Addictive, Substance-Related, and Co-occuring Conditions. 3rd ed. The Change Companies; 2013.
5. Substance Abuse and Mental Health Services Administration. Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2014.
6. Degenhardt L, Randall D, Hall W, et al. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. *Drug Alcohol Depend* 2009;105:9–15.
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-III. Washington, D.C.: American Psychiatric Association; 1980.
8. Compton WM, Dawson DA, Goldstein RB, et al. Crosswalk between DSM-IV dependence and DSM-5 substance use disorders for opioids, cannabis, cocaine and alcohol. *Drug Alcohol Depend* 2013;132:387–390.
9. Substance Abuse and Mental Health Services Administration. Drug Addiction Treatment Act, full text. 2000. Available at: http://buprenorphine.samhsa.gov/fulllaw.html.
10. American Society on Addiction Medicine. The ASAM Standards of Care for the Addiction Specialist Physician. 2014. Available at: http://www.asam.org/docs/default-source/practice-support/quality-improvement/asam-standards-of-care.pdf?sfvrsn=10.
11. Hagan J, Shaw J, Duncan P, eds. Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents. Pocket Guide. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2008.
12. National Alliance on Mental Illness. Psychosocial Treatments. 2014. Available at: https://http://www.nami.org/Learn-More/Treatment/Psychosocial-Treatments. Accessed February 2, 2015.
13. National Institute on Drug Abuse. Principles of Drug Addiction Treatment: A Research-based Guide. Bethesda, MD: National Institute on Drug Abuse; 2009.
14. Substance Abuse and Mental Health Services Administration. Treatment Improvement Protocol Series 42: Substance abuse treatment for persons with co-occuring disorders. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2008.
15. Substance Abuse and Mental Health Services Administration. Treatment Improvement Protocol Series 45: Detoxification and Substance Abuse Treatment. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2006.
16. American Congress of Obstetricians and Gynecologists. Pregnant Women and Prescription Drug Abuse, Dependence and Addiction. Toolkit on State Legislation. ACOG; 2014.
17. Moderation Management. What is moderation management? Available at: http://moderation.org/whatisMM.shtml. Accessed February 2, 2015.
18. World Health Organization. Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence. Department of Mental Health, Substance Abuse and World Health Organization; 2009.
19. Sigmon SC, Bisaga A, Nunes EV, et al. Opioid detoxification and naltrexone induction strategies: recommendations for clinical practice. *Am J Drug Alcohol Abuse* 2012;38:187–199.
20. Drug Enforcement Administration. Drugs of Abuse: a DEA Resource Guide. 2011. Available at: http://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf.
21. US Food and Drug Administration. Sleep disorder (sedative-hypnotic) drug information. 2015; Available at: http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm101557.htm.
22. Types of withdrawal. Buppractice Web site. Available at: http://www.buppractice.com/node/4818.
23. Muhuri PK, Gfroerer JC, Davies MC. Associations of Nonmedical Pain Reliever Use and Initiation of Heroin Use in the US. Rockville, MD: Center for Behavioral Health Statistics and Quality Data Review; 2013.
24. Paulozzi LJ, Zhang K, Jones CM, et al. Risk of adverse health outcomes with increasing duration and regularity of opioid therapy. *J Am Board Fam Med* 2014;27:329–338.
25. Nelson PK, Mathers BM, Cowie B, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet* 2011;378:571–583.

26. Fitch K BS, Bernstein SJ, Aguilar MD, et al. The Rand/UCLA Appropriateness Method User's Manual. Rand Corporation; 2001.

27. Drummond D, Perryman K. Psychosocial Interventions in Pharmacotherapy of Opioid Dependence: a Literature Review. London: St George's University of London, Division of Mental Health, Section of Addictive Behaviour; 2007.

28. Amato L, Minozzi S, Davoli M, et al. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database Syst Rev* 2011. CD005031.

29. Amato L, Minozzi S, Davoli M, et al. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. *Cochrane Database Syst Rev* 2011. CD004147.

30. Ghitza UE, Epstein DH, Preston KL. Nonreporting of cannabis use: predictors and relationship to treatment outcome in methadone maintained patients. *Addict Behav* 2007;32:938–949.

31. Lions C, Carrieri MP, Michel L, et al. Predictors of non-prescribed opioid use after one year of methadone treatment: an attributable-risk approach (ANRS-Methaville trial). *Drug Alcohol Depend* 2014;135:1–8.

32. Preston KL, Silverman K, Higgins ST, et al. Cocaine use early in treatment predicts outcome in a behavioral treatment program. *J Consult Clin Psychol* 1998;66:691–696.

33. Johnson RE, Eissenberg T, Stitzer ML, et al. A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence. *Drug Alcohol Depend* 1995;40:17–25.

34. Mattick RP, Breen C, Kimber J, et al. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev* 2009. CD002209.

35. Prochaska JJ, Delucchi K, Hall SM. A meta-analysis of smoking cessation interventions with individuals in substance abuse treatment or recovery. *J Consult Clin Psychol* 2004;72:1144–1156.

36. Baca CT, Yahne CE. Smoking cessation during substance abuse treatment: what you need to know. *J Subst Abuse Treat* 2009;36:205–219.

37. Tsoh JY, Chi FW, Mertens JR, et al. Stopping smoking during first year of substance use treatment predicted 9-year alcohol and drug treatment outcomes. *Drug Alcohol Depend* 2011;114:110–118.

38. Handelsman L, Cochrane KJ, Aronson MJ, et al. Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse* 1987;13:293–308.

39. Center for Substance Abuse Treatment. Federal Guidelines for Opioid Treatment. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013. http://dpt.samhsa.gov/pdf/FederalGuidelinesforOpioidTreatment5-6-2013revisiondraft_508.pdf.

40. American Society of Addiction Medicine. Drug Testing: a White Paper of the American Society of Addiction Medicine; 2013. Available at: http://www.asam.org/docs/default-source/publicy-policy-statements/drug-testing-a-white-paper-by-asam.pdf?sfvrsn=0.

41. Mattick R, Breen C, Kimber J, et al. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev* 2009. CD002209.

42. Vanichseni S, Wongsuwan B, Choopanya K, et al. A controlled trial of methadone maintenance in a population of intravenous drug users in Bangkok: implications for prevention of HIV. *Int J Addict* 1991;26:1313–1320.

43. Newman RG, Whitehill WB. Double-blind comparison of methadone and placebo maintenance treatments of narcotic addicts in Hong Kong. *Lancet* 1979;2:485–488.

44. Ling W, Charuvastra C, Collins JF, et al. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction* 1998;93:475–486.

45. Comer SD, Sullivan MA, Yu E, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Arch Gen Psychiatry* 2006;63:210–218.

46. Krupitsky E, Nunes E, Ling W, et al. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet* 2011;377:1506–1513.

47. Syed YY, Keating GM. Extended-release intramuscular naltrexone (VIVITROL(R)): a review of its use in the prevention of relapse to opioid dependence in detoxified patients. *CNS Drugs* 2013;27:851–861.

48. Soyka M, Apelt S, Lieb M, et al. One-year mortality rates of patients receiving methadone and buprenorphine maintenance therapy: a nationally representative cohort study in 2694 patients. *J Clin Psychopharmacol* 2006;26:657–660.

49. Harrison Narcotic Act of 1914, Pub. L. No. 63-223, 38 Stat. 785, repealed by Comprehensive Drug Abuse Prevention and Control Act of 1970, Pub. L. No. 91-513, 84 Stat. 1236 (codified as amended at 21 U.S.C. §§ 801–971).

50. Krupitsky E, Nunes EV, Ling W, et al. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet* 2011;377:1506–1513.

51. Cheskin LJ, Fudala PJ, Johnson RE. A controlled comparison of buprenorphine and clonidine for acute detoxification from opioids. *Drug Alcohol Depend* 1994;36:115–121.

52. Bickel WK, Stitzer ML, Bigelow GE, et al. A clinical trial of buprenorphine: comparison with methadone in the detoxification of heroin addicts. *Clin Pharmacol Ther* 1988;43:72–78.

53. Ling W, Amass L, Shoptaw S, et al. A multi-center randomized trial of buprenorphine-naloxone versus clonidine for opioid detoxification: findings from the National Institute on Drug Abuse Clinical Trials Network. *Addiction* 2005;100:1090–1100.

54. Sigmon SC, Dunn KE, Saulsgiver K, et al. A randomized, double-blind evaluation of buprenorphine taper duration in primary prescription opioid abusers. *J Am Med Assoc Psychiatry* 2013;70:1347–1354.

55. Saxon AJ, Ling W, Hillhouse M, et al. Buprenorphine/Naloxone and methadone effects on laboratory indices of liver health: a randomized trial. *Drug Alcohol Depend* 2013;128:71–76.

56. BUNAVAIL [package insert]. Raleigh, NC: BioDelivery Sciences International, Inc.; Revised June 2014.

57. SUBOXONE [package insert]. Richmond, VA: Reckitt Benckiser Pharmaceuticals Inc.; Revised April 2014.

58. ZUBSOLV [package insert]. Morristown, NJ: Orexo US, Inc.; Revised December 2014.

59. Minozzi S, Amato L, Vecchi S, et al. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev* 2006. CD001333.

60. Hassanian-Moghaddam H, Afzali S, Pooya A. Withdrawal syndrome caused by naltrexone in opioid abusers. *Hum Exp Toxicol* 2014;33:561–567.

61. Ruan X, Chen T, Gudin J, et al. Acute opioid withdrawal precipitated by ingestion of crushed embeda (morphine extended release with sequestered naltrexone): case report and the focused review of the literature. *J Opioid Manag* 2010;6:300–303.

62. Fishman M. Precipitated withdrawal during maintenance opioid blockade with extended release naltrexone. *Addiction* 2008;103:1399–1401.

63. Katz EC, Brown BS, Schwartz RP, et al. Transitioning opioid-dependent patients from detoxification to long-term treatment: efficacy of intensive role induction. *Drug Alcohol Depend* 2011;117:24–30.

64. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs* 2003;35:253–259.

65. Day E, Strang J. Outpatient versus inpatient opioid detoxification: a randomized controlled trial. *J Subst Abuse Treat* 2011;40:55–66.

66. Collins ED, Kleber HD, Whittington RA, et al. Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial. *J Am Med Assoc* 2005;294:903–913.

67. Kienbaum P, Scherbaum N, Thurauf N, et al. Acute detoxification of opioid-addicted patients with naloxone during propofol or methohexital anesthesia: a comparison of withdrawal symptoms, neuroendocrine, metabolic, and cardiovascular patterns. *Crit Care Med* 2000;28:969–976.

68. American Society of Addiction Medicine. Public policy statement on rapid and ultra rapid opioid detoxification. 2005. http://www.asam.org/docs/publicy-policy-statements/1rod-urod—rev-of-oadusa-4-051.pdf?sfvrsn=0.

69. Hamilton RJ, Olmedo RE, Shah S, et al. Complications of ultrarapid opioid detoxification with subcutaneous naltrexone pellets. *Acad Emerg Med* 2002;9:63–68.

70. Centers for Disease Control. Deaths and Severe Adverse Events Associated with Anesthesia-Assisted Rapid Opioid Detoxification: New York City, 2012. Morbidity and Mortality Weekly; 2013. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6238a1.htm.

71. Gowing L, Ali R, White JM. Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. *Cochrane Database Syst Rev* 2010. CD002022.

72. Baxter LE, Sr Campbell A, Deshields M, et al. Safe methadone induction and stabilization: report of an expert panel. *J Addict Med* 2013;7:377–386.

73. Eap CB, Bourquin M, Martin J, et al. Plasma concentrations of the enantiomers of methadone and therapeutic response in methadone maintenance treatment. *Drug Alcohol Depend* 2000;61:47–54.

74. Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. *Clin Pharmacokinet* 2002;41:1153–1193.

75. Leavitt SB, Shinderman MD, Maxwell S, et al. When 'enough' is not enough: new perspectives on optimal methadone maintenance dose. *Mount Sinai J Med* 2000;67:404–411.

76. Loimer N, Schmid R. The use of plasma levels to optimize methadone maintenance treatment. *Drug Alcohol Depend* 1992;30:241–246.

77. Strain EC, Bigelow GE, Liebson IA, et al. Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial. *J Am Med Assoc* 1999;281:1000–1005.

78. Strain EC, Stitzer ML, Liebson IA, et al. Dose-response effects of methadone in the treatment of opioid dependence. *Ann Intern Med* 1993;119:23–27.

79. Ehret GB, Voide C, Gex-Fabry M, et al. Drug-induced long QT syndrome in injection drug users receiving methadone: high frequency in hospitalized patients and risk factors. *Arch Intern Med* 2006;166:1280–1287.

80. US Food and Drug Administration. Information for Healthcare Professionals Methadone Hydrochloride: Text Version. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142841.htm. Accessed January 12, 2015.

81. Cohen SP, Mao J. Concerns about consensus guidelines for QTc interval screening in methadone treatment. *Ann Intern Med* 2009;151:216–217. author reply 218–219.

82. VIVITROL [package insert]. Waltham, MA: Alkermes, Inc.; Revised July 2013.

83. Parran TV, Adelman CA, Merkin B, et al. Long-term outcomes of office-based buprenorphine/naloxone maintenance therapy. *Drug Alcohol Depend* 2010;106:56–60.

84. Gunderson EW, Wang XQ, Fiellin DA, et al. Unobserved versus observed office buprenorphine/naloxone induction: a pilot randomized clinical trial. *Addict Behav* 2010;35:537–540.

85. Yokell MA, Zaller ND, Green TC, Rich JD. Buprenorphine and buprenorphine/naloxone diversion, misuse, and illicit use: an international review. Curr Drug Abuse Rev 2011;4:28–41.

86. National Institutes of Health. Buprenorphine Sublingual. What Should I Know About Storage and Disposal of This Medication? 2012. Available at: http://www.nlm.nih.gov/medlineplus/druginfo/meds/a605002.html - storage-conditions.

87. Mannelli P, Peindl KS, Lee T, et al. Buprenorphine-mediated transition from opioid agonist to antagonist treatment: state of the art and new perspectives. *Curr Drug Abuse Rev* 2012;5:52–63.

88. Minozzi S, Amato L, Vecchi S, et al. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev* 2011. CD001333.

89. Adi Y, Juarez-Garcia A, Wang D, et al. Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation. *Health Technol Assess* 2007;11. iii–iv, 1–85.

90. Tiihonen J, Krupitsky E, Verbitskaya E, et al. Naltrexone implant for the treatment of polydrug dependence: a randomized controlled trial. *Am J Psychiatry* 2012;169:531–536.

91. Strang J, McCambridge J, Best D, et al. Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study. *Br Med J* 2003;326:959–960.

92. American Society of Addiction Medicine. Public Policy Statement on the Relationship Between Treatment and Self Help: a Joint Statement of the American Society of Addiction Medicine, the American Academy of Addiction Psychiatry, and the American Psychiatric Association. 1997. http://www.asam.org/docs/publicy-policy-statements/1treatment-and-self-help—joint-12-971.pdf?sfvrsn=0.

93. Dutra L, Stathopoulou G, Basden SL, et al. A meta-analytic review of psychosocial interventions for substance use disorders. *Am J Psychiatry* 2008;165:179–187.

94. Brigham GS, Slesnick N, Winhusen TM, et al. A randomized pilot clinical trial to evaluate the efficacy of Community Reinforcement and Family Training for Treatment Retention (CRAFT-T) for improving outcomes for patients completing opioid detoxification. *Drug Alcohol Depend* 2014;138:240–243.

95. Ruetsch C, Tkacz J, McPherson TL, et al. The effect of telephonic patient support on treatment for opioid dependence: outcomes at one year follow-up. *Addict Behav* 2012;37:686–689.

96. Fiellin DA, Barry DT, Sullivan LE, et al. A randomized trial of cognitive behavioral therapy in primary care-based buprenorphine. *Am J Med* 2013;126:74.e11–74.e17.

97. Fiellin DA, Pantalon MV, Chawarski MC, et al. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. *N Engl J Med* 2006;355:365–374.

98. Tetrault JM, Moore BA, Barry DT, et al. Brief versus extended counseling along with buprenorphine/naloxone for HIV-infected opioid dependent patients. *J Subst Abuse Treat* 2012;43:433–439.

99. Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Arch Gen Psychiatry* 2011;68:1238–1246.

100. Committee on Health Care for Underserved Women, American Society of Addiction Medicine. ACOG Committee Opinion No. 524: Opioid abuse, dependence, and addiction in pregnancy. *Obstet Gynecol* 2012;119:1070–1076.

101. Chasnoff IJ, Landress HJ, Barrett ME. The prevalence of illicit-drug or alcohol use during pregnancy and discrepancies in mandatory reporting in Pinellas County. *Florida N Engl J Med* 1990;322:1202–1206.

102. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 2010;363:2320–2331.

103. Wiegand SL, Stringer EM, Stuebe AM, et al. Buprenorphine and naloxone compared with methadone treatment in pregnancy. *Obstet Gynecol* 2015;125:363–368.

104. Debelak K, Morrone WR, O'Grady KE, et al. Buprenorphine + naloxone in the treatment of opioid dependence during pregnancy-initial patient care and outcome data. *Am J Addict* 2013;22:252–254.

105. Burns L, Mattick RP, Lim K, et al. Methadone in pregnancy: treatment retention and neonatal outcomes. *Addiction* 2007;102:264–270.

106. Kreek MJ. Methadone disposition during the perinatal period in humans. *Pharmacol Biochem Behav* 1979;11(Suppl):7–13.

107. Wolff K, Boys A, Rostami-Hodjegan A, et al. Changes to methadone clearance during pregnancy. *Eur J Clin Pharmacol* 2005;61:763–768.

108. Nekhayeva IA, Nanovskaya TN, Deshmukh SV, et al. Bidirectional transfer of methadone across human placenta. *Biochem Pharmacol* 2005;69:187–197.

109. Substance Abuse and Mental Health Services Administration. Treatment Improvement Protocol Series 2: Pregnant, Substance-Using Women. Rockville, MD: Substance Abuse and Mental Health Services Administration; 1995.

110. Swift RM, Dudley M, DePetrillo P, et al. Altered methadone pharmacokinetics in pregnancy: implications for dosing. *J Subst Abuse* 1989;1:453–460.

111. Cleary BJ, Donnelly J, Strawbridge J, et al. Methadone dose and neonatal abstinence syndrome-systematic review and meta-analysis. *Addiction* 2010;105:2071–2084.

112. McCarthy JJ, Leamon MH, Willits NH, et al. The effect of methadone dose regimen on neonatal abstinence syndrome. *J Addict Med* 2015;9:105–110.

113. Academy of Breastfeeding Medicine Protocol Committee, Jansson L. ABM clinical protocol #21: guidelines for breastfeeding and the drug-dependent woman. Breastfeed Med 2009;4:225–228.

114. Abdel-Latif ME, Pinner J, Clews S, et al. Effects of breast milk on the severity and outcome of neonatal abstinence syndrome among infants of drug-dependent mothers. *Pediatrics* 2006;117:e1163–e1169.

115. Ballard JL. Treatment of neonatal abstinence syndrome with breast milk containing methadone. *J Perinat Neonatal Nurs* 2002;15:76–85.

116. Liu AJ, Nanan R. Methadone maintenance and breastfeeding in the neonatal period. *Pediatrics* 2008;121:106–114.

117. Ilett KF, Hackett LP, Gower S, et al. Estimated dose exposure of the neonate to buprenorphine and its metabolite norbuprenorphine via breastmilk during maternal buprenorphine substitution treatment. *Breastfeed Med* 2012;7:269–274.

118. Hines S, Theodorou S, Williamson A, et al. Management of acute pain in methadone maintenance therapy in-patients. *Drug Alcohol Rev* 2008;27:519–523.

119. Rubenstein RB, Spira I, Wolff WI. Management of surgical problems in patients on methadone maintenance. *Am J Surg* 1976;131:566–569.
120. Scimeca MM, Savage SR, Portenoy R, et al. Treatment of pain in methadone-maintained patients. *Mt Sinai J Med* 2000;67:412–422.
121. Vadivelu N, Mitra S, Kaye AD, et al. Perioperative analgesia and challenges in the drug-addicted and drug-dependent patient. *Best Pract Res Clin Anaesthesiol* 2014;28:91–101.
122. Pade PA, Cardon KE, Hoffman RM, et al. Prescription opioid abuse, chronic pain, and primary care: a Co-occurring Disorders Clinic in the chronic disease model. *J Subst Abuse Treat* 2012;43:446–450.
123. Daitch D, Daitch J, Novinson D, et al. Conversion from high-dose full-opioid agonists to sublingual buprenorphine reduces pain scores and improves quality of life for chronic pain patients. *Pain Med* 2014;15:2087–2094.
124. Bryson EO. The perioperative management of patients maintained on medications used to manage opioid addiction. *Curr Opin Anaesthesiol* 2014;27:359–364.
125. Macintyre PE, Russell RA, Usher KA, et al. Pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy. *Anaesth Intensive Care* 2013;41:222–230.
126. McCormick Z, Chu SK, Chang-Chien GC, et al. Acute pain control challenges with buprenorphine/naloxone therapy in a patient with compartment syndrome secondary to McArdle's disease: a case report and review. *Pain Med* 2013;14:1187–1191.
127. Minozzi S, Amato L, Bellisario C, et al. Detoxification treatments for opiate dependent adolescents. *Cochrane Database Syst Rev* 2014;4:CD006749.
128. Minozzi S, Amato L, Bellisario C, et al. Maintenance treatments for opiate-dependent adolescents. *Cochrane Database Syst Rev* 2014;6:CD007210.
129. Ford CA, Millstein SG, Halpern-Felsher BL, et al. Influence of physician confidentiality assurances on adolescents' willingness to disclose information and seek future health care. A randomized controlled trial. *J Am Med Assoc* 1997;278:1029–1034.
130. Hallfors DD, Waller MW, Ford CA, et al. Adolescent depression and suicide risk: association with sex and drug behavior. *Am J Prev Med* 2004;27:224–231.
131. Weddle M, Kokotailo PK. Confidentiality and consent in adolescent substance abuse: an update. *Virtual Mentor* 2005. 7(3).
132. Substance Abuse and Mental Health Services Administration. Treatment Improvement Protocol Series 33: Treatment for Stimulant Use Disorders. Rockville, MD: Substance Abuse and Mental Health Services Administration; 1999.
133. Substance Abuse and Mental Health Services Administration. Federal Guidelines for Opioid Treatment, 2013 revision, draft. Available at: http://www.dpt.samhsa.gov/pdf/FederalGuidelinesforOpioidTreatment5-6-2013revisiondraft_508.pdf.
134. Hopfer CJ, Khuri E, Crowley TJ, et al. Adolescent heroin use: a review of the descriptive and treatment literature. *J Subst Abuse Treat* 2002;23:231–237.
135. Marsch LA, Bickel WK, Badger GJ, et al. Comparison of pharmacological treatments for opioid-dependent adolescents: a randomized controlled trial. *Arch Gen Psychiatry* 2005;62:1157–1164.
136. Woody GE, Poole SA, Subramaniam G, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. *J Am Med Assoc* 2008;300:2003–2011.
137. Fishman MJ, Winstanley EL, Curran E, et al. Treatment of opioid dependence in adolescents and young adults with extended release naltrexone: preliminary case-series and feasibility. *Addiction* 2010;105:1669–1676.
138. Brooner RK, King VL, Kidorf M, et al. Psychiatric and substance use comorbidity among treatment-seeking opioid abusers. *Arch Gen Psychiatry* 1997;54:71–80.
139. Chambers RA, Bickel WK, Potenza MN. A scale-free systems theory of motivation and addiction. *Neurosci Biobehav Rev* 2007;31:1017–1045.
140. Krystal JH, D'Souza DC, Gallinat J, et al. The vulnerability to alcohol and substance abuse in individuals diagnosed with schizophrenia. *Neurotox Res* 2006;10:235–252.
141. Bradizza CM, Stasiewicz PR, Paas ND. Relapse to alcohol and drug use among individuals diagnosed with co-occurring mental health and substance use disorders: a review. *Clin Psychol Rev* 2006;26:162–178.
142. Khantzian EJ. The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *Am J Psychiatry* 1985;142:1259–1264.
143. Lybrand J, Caroff S. Management of schizophrenia with substance use disorders. *Psychiatr Clin North Am* 2009;32:821–833.
144. Gvion Y, Apter A. Suicide and suicidal behavior. *Public Health Rev* 2012;34:1–20.
145. Bertolote J, Fleischmann A, De Leo D, et al. Psychiatric diagnoses and suicide: revisiting the evidence. *Crisis* 2004;25:147–155.
146. Brunette MF, Mueser KT. Psychosocial interventions for the long-term management of patients with severe mental illness and co-occurring substance use disorder. *J Clin Psychiatry* 2006;67(Suppl 7):10–17.
147. Dixon LB, Dickerson F, Bellack AS, et al. The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. *Schizophr Bull* 2010;36:48–70.
148. Himelhoch S, Lehman A, Kreyenbuhl J, et al. Prevalence of chronic obstructive pulmonary disease among those with serious mental illness. *Am J Psychiatry* 2004;161:2317–2319.
149. Jurgens R, Ball A, Verster A. Interventions to reduce HIV transmission related to injecting drug use in prison. *Lancet Infect Dis* 2009;9:57–66.
150. Justice Policy Institute. Substance Abuse Treatment and Public Safety; 2008. Available at: http://www.justicepolicy.org/images/upload/08_01_rep_drugtx_ac-ps.pdf.
151. Dolan KA, Wodak AD, Hall WD. Methadone maintenance treatment reduces heroin injection in New South Wales prisons. *Drug Alcohol Rev* 1998;17:153–158.
152. Strang J, Gossop M, Heuston J, et al. Persistence of drug use during imprisonment: relationship of drug type, recency of use and severity of dependence to use of heroin, cocaine and amphetamine in prison. *Addiction* 2006;101:1125–1132.
153. Stover H, Michels II. Drug use and opioid substitution treatment for prisoners. *Harm Reduct J* 2010;7:1–7.
154. Cropsey KL, Villalobos GC, St Clair CL. Pharmacotherapy treatment in substance-dependent correctional populations: a review. *Subst Use Misuse* 2005;40:1983–1999. 2043-1988.
155. Darke S, Kaye S, Finlay-Jones R. Drug use and injection risk-taking among prison methadone maintenance patients. *Addiction* 1998;93:1169–1175.
156. Dolan KA, Shearer J, White B, et al. Four-year follow-up of imprisoned male heroin users and methadone treatment: mortality, re-incarceration and hepatitis C infection. *Addiction* 2005;100:820–828.
157. Heimer R, Catania H, Newman RG, et al. Methadone maintenance in prison: evaluation of a pilot program in Puerto Rico. *Drug Alcohol Depend* 2006;83:122–129.
158. Bertram S GA. Views of Recidivists Released After Participating in the N.S.W. Prison Methadone Program and the Problems They Faced in the Community. Sydney, Australia: Department of Corrective Services; 1990.
159. Canada ARCRBCS. Institutional methadone maintenance treatment: impact on release outcome and institutional behaviour. Ottawa, ON, Canada. Available at: http://198.103.98.138/text/rsrch/reports/r119/r119_e.pdf.
160. Magura S, Lee JD, Hershberger J, et al. Buprenorphine and methadone maintenance in jail and post-release: a randomized clinical trial. *Drug Alcohol Depend* 2009;99:222–230.
161. Gordon MS, Kinlock TW, Schwartz RP, et al. A randomized controlled trial of prison-initiated buprenorphine: prison outcomes and community treatment entry. *Drug Alcohol Depend* 2014;142:33–40.
162. Coviello DM, Cornish JW, Lynch KG, et al. A multisite pilot study of extended-release injectable naltrexone treatment for previously opioid-dependent parolees and probationers. *Subst Abus* 2012;33:48–59.
163. National Commission on Correctional Health Care. Standards for Opioid Treatment Programs in Correctional Facilities. NCCHC; 2004. http://www.ncchc.org/standards.
164. Clarke SF, Dargan PI, Jones AL. Naloxone in opioid poisoning: walking the tightrope. *Emerg Med J* 2005;22:612–616.
165. Centers for Disease Control. Injury Prevention and Control: Data and Statistics (WISQARS). Available at: http://www.cdc.gov/injury/wisqars/.
166. Law Atlas Map. Public Health Law Research Law Atlas Web site. http://www.lawatlas.org/query?dataset=laws-regulating-administration-of-naloxonexc.
167. American Society of Addiction Medicine. Public policy statement on the use of naloxone for the prevention of drug overdose deaths; 2010. Available

at: http://www.asam.org/docs/default-source/publicly-policy-statements/1naloxone-rev-8-14.pdf?sfvrsn=0. Accessed January 31, 2015.

168. Substance Abuse and Mental Health Services Administration. Opioid Overdose Prevention Toolkit - Updated 2014; 2014. Available at: http://store.samhsa.gov/product/Opioid-Overdose-Prevention-Toolkit-Updated- 2014/SMA14-4742.

169. Boyer EW. Management of opioid analgesic overdose. *N Engl J Med* 2012;367:146–155.

170. Dahan A, Aarts L, Smith TW. Incidence, reversal, and prevention of opioid-induced respiratory depression. *Anesthesiology* 2010;112:226–238.

171. Kelly AM, Kerr D, Dietze P, et al. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. *Med J Aust* 2005;182:24–27.

172. Kerr D, Kelly AM, Dietze P, et al. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. *Addiction* 2009;104:2067–2074.

173. Robinson A, Wermeling DP. Intranasal naloxone administration for treatment of opioid overdose. *Am J Health Syst Pharm* 2014;71:2129–2135

APPENDICES

Appendix I: Clinical References Reviewed

Baltimore Buprenorphine Initiative. Clinical guidelines for buprenorphine treatment of opioid dependence in the Baltimore Buprenorphine Initiative. Baltimore, MD; 2011.

Bell J, Kimber J, Lintzeris N, et al. Clinical guidelines and procedures for the use of naltrexone in the management of opioid dependence. Commonwealth of Australia: National Drug Strategy; 2003.

Bell, J. The role of supervision of dosing in opioid maintenance treatment. London: National Addiction Centre; 2007.

Brooking, A. Guidelines for the management of opiate dependent patients at RCHT. Royal Cornwall Hospitals: NHS; 2010.

Chou R, Cruciani RA, Fiellin DA, et al. 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. 2014;15(4):321–337.

Chou R, Weimer MB, Dana T. Methadone overdose and cardiac arrhythmia potential: Findings from a review of evidence for an American Pain Society and College on Problems of Drug Dependence Clinical Practice Guideline. J Pain. 2014; 15(4):338–365.

Committee on Health Care for Underserved Women and the American Society of Addiction Medicine. Opioid abuse, dependence, and addiction in pregnancy. 2012; Committee Opinion Number 524.

Department of Health (England) and the Devolved Administrations. Drug misuse and dependence: UK guidelines on clinical management. London: Department of Health (England), the Scottish Government, Welsh Assembly Government and Northern Ireland Executive; 2007.

Federal Bureau of Prisons Clinical Practice Guidelines. Detoxification of Chemically Dependent Inmates. Washington, DC; 2009.

Ford A. WPCT Guidelines- Methadone and Buprenorphine in the Management of Opioid Dependence. Prescribing Guidelines for the Young Person's Substance Use Service—SPACE. Worchester: NHS; 2009.

Ford C, Halliday K, Lawson E, Browne E. Guidance for the use of substitute prescribing in the treatment of opioid dependence in primary care. London: Royal College of General Practitioners; 2011.

Gowing L, Ali R, Dunlap A, Farrell M, Lintzeris N. National guidelines for medication-assisted treatment of opioid dependence. Commonwealth of Australia; 2014.

Handford C, Kahan M, Lester MD, & Ordean A. Buprenorphine/naloxone for opioid dependence: Clinical practice guideline. Canada: Centre for Addiction and Mental Health; 2012.

Hanna, M. Supporting Recovery from Opioid Addiction: Community Care Best Practice Guidelines for Buprenorphine and Suboxone®. USA: Community Care Behavioral Health Organization; 2013.

Henry-Edwards S, Gowing L, White J, et al. Clinical Guidelines and Procedures for the Use of Methadone in the Maintenance Treatment of Opioid Dependence. Commonwealth of Australia: National Drug Strategy; 2003.

Hudak ML, Tan RC. The Committee on Drugs, & The Committee on Fetus and Newborn. Neonatal Drug Withdrawal. Pediatrics. 2012;129(2):e540–560.

Johnston A, Mandell TW, Meyer M. Treatment of Opioid Dependence in Pregnancy: Vermont Guidelines. Burlington: VT; 2010.

Lintzeris N, Clark N, Muhleisen P, et al. Clinical guidelines: buprenorphine treatment of heroin dependence. Commonwealth of Australia: Public Health Division; 2003.

The Management of Substance Use Disorder Working Group. VA/DoD Clinical Practice Guideline for management of substance use disorders (SUDs). Version 2.0; 2009.

Ministry of Health. New Zealand Clinical Guidelines for the Use of Buprenorphine (with or without Naloxone) in the Treatment of Opioid Dependence. Wellington: Ministry of Health; 2010.

Ministry of Health. Practice Guidelines for Opioid Substitution Treatment in New Zealand 2008. Wellington: Ministry of Health; 2008.

Nicholls L, Bragaw L, Ruetsch C. Opioid Dependence Treatment and Guidelines. J Manag Care Pharm. 2010; 16(Suppl1b):S14–S21.

Stephenson D. Guideline for physicians working in California opioid treatment programs. San Francisco, CA: California Society of Addiction Medicine. CSAM Committee on Treatment of Opioid Dependence; 2008.

Substance Abuse and Mental Health Services Administration. (2012). An Introduction to Extended-Release Injectable Naltrexone for the Treatment of People With Opioid Dependence. Advisory. 2012;11(1):1–8.

Substance Abuse and Mental Health Services Administration. Addressing Viral Hepatitis in People With Substance Use Disorders. Treatment Improvement Protocol (TIP) Series 53. HHS Publication No. (SMA) 11-4656. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2011.

Substance Abuse and Mental Health Services Administration Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville,

MD: Substance Abuse and Mental Health Services Administration; 2004.

Substance Abuse and Mental Health Service Administration Center for Substance Abuse Treatment. Detoxification and Substance Abuse Treatment. Treatment Improvement Protocol (TIP) Series 45. DHHS Publication No. (SMA) 06-4131. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2006.

Substance Abuse and Mental Health Service Administration Center for Substance Abuse Treatment. 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; 2005.

Substance Abuse and Mental Health Services Administration. Quick Guide for Physicians Based on Tip 40: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 05-4003. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2005.

The College of Physicians and Surgeons of Ontario. Methadone Maintenance Treatment Program Standards and Clinical Guidelines. 4th ed. Toronto, Ontario; 2011.

Verster A, Buning E. Methadone Guidelines. Amsterdam: Netherlands: Euro-Meth; 2000.

Vermont Department of Health. Vermont Buprenorphine Practice Guidelines. Burlington, VT; 2010.

Weimer MB, Chou R. Research gaps on methadone harms and comparative harms: findings from a review of the evidence for an American Pain Society and College on Problems of Drug Dependence Clinical Practice Guideline. J Pain. 2014; 15(4): 366–376.

World Health Organization. Department of Mental Health, Substance Abuse and World Health Organization. Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. World Health Organization; 2009.

Appendix II: Bioequivalence Information and Charts

Bioequivalence of Suboxone® (buprenorphine and naloxone) Sublingual Tablets and Suboxone Sublingual Film

Patients being switched between Suboxone® (buprenorphine and naloxone) sublingual tablets and Suboxone® sublingual film should be started on the same dosage as the previously administered product. However, dosage adjustments may be necessary when switching between products. Not all strengths and combinations of the Suboxone® sublingual films are bioequivalent to Suboxone® (buprenorphine and naloxone) sublingual tablets as observed in pharmacokinetic studies. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to film, or vice-versa. Patients should be monitored for symptoms related to over-dosing or under-dosing.

In pharmacokinetic studies, the 2 mg/0.5 mg and 4 mg/1 mg doses administered as Suboxone® sublingual films showed comparable relative bioavailability to the same total dose of Suboxone® (buprenorphine and naloxone) sublingual tablets, whereas the 8 mg/2 mg and 12 mg/3 mg doses administered as Suboxone® sublingual films showed higher relative bioavailability for both buprenorphine and naloxone compared to the same total dose of Suboxone® (buprenorphine and naloxone) sublingual tablets. A combination of one 8 mg/2 mg and two 2 mg/0.5 mg Suboxone® sublingual films (total dose of 12 mg/ 3 mg) showed comparable relative bioavailability to the same total dose of Suboxone® (buprenorphine and naloxone) sublingual tablets.

Switching between Suboxone® (buprenorphine and naloxone) Sublingual Film and Suboxone® Sublingual Tablets

Because of the potentially greater relative bioavailability of Suboxone® sublingual film compared to Suboxone® (buprenorphine and naloxone) sublingual tablets, patients switching from Suboxone® (buprenorphine and naloxone) sublingual tablets to Suboxone® sublingual film should be monitored for over-medication. Those switching from Suboxone® sublingual film to Suboxone® (buprenorphine and naloxone) sublingual tablets should be monitored for withdrawal or other indications of under-dosing. In clinical studies, pharmacokinetics of Suboxone® sublingual film were similar to the respective dosage strengths of Suboxone® (buprenorphine and naloxone) sublingual tablets, although not all doses and dose combinations met bioequivalence criteria.

Switching between Suboxone® Sublingual Tablets or Films and Bunavail® Buccal Film

The difference in bioavailability of Bunavail® compared to Suboxone® sublingual tablet requires a different dosage strength to be administered to the patient. A Bunavail® 4.2/0.7 mg buccal film provides equivalent buprenorphine exposure to a Suboxone® 8/2 mg sublingual tablet. Patients being switched between Suboxone® dosage strengths and Bunavail® dosage strengths should be started on the corresponding dosage as defined below:

Suboxone® Sublingual Tablet Dosage Strength	Corresponding Bunavail® Buccal Film Strength
4/1 mg buprenorphine/naloxone	2.1/0.3 mg buprenorphine/naloxone
8/2 mg buprenorphine/naloxone	4.2/0.7 mg buprenorphine/naloxone
12/3 mg buprenorphine/naloxone	6.3/1 mg buprenorphine/naloxone

Dosage and Administration of Zubsolv®

The difference in bioavailability of Zubsolv® compared to Suboxone® tablet requires a different tablet strength to be given to the patient. One Zubsolv® 5.7/1.4 mg sublingual tablet provides equivalent buprenorphine exposure to one Suboxone® 8/2 mg sublingual tablet. The corresponding doses ranging from induction to maintenance treatment are:

Induction phase: Final sublingual buprenorphine dose	Maintenance phase: Corresponding sublingual Zubsolv® dose
8 mg buprenorphine, taken as:	5.7 mg/1.4 mg Zubsolv®, taken as:
• One 8 mg buprenorphine tablet	• One 5.7 mg/1.4 mg Zubsolv® tablet
12 mg buprenorphine, taken as:	8.6 mg/2.1 mg Zubsolv®, taken as:
• One 8 mg buprenorphine tablet AND	• One 8.6 mg/2.1 mg Zubsolv® tablet
• Two 2 mg buprenorphine tablets	
16 mg buprenorphine, taken as:	11.4 mg/2.9 mg Zubsolv®, taken as:
• Two 8 mg buprenorphine tablets	• One 11.4/2.9 mg Zubsolv® tablet

Switching between Zubsolv® Sublingual Tablets and other buprenorphine/naloxone combination products

For patients being switched between Zubsolv® sublingual tablets and other buprenorphine/naloxone products dosage adjustments may be necessary. Patients should be monitored for over-medication as well as withdrawal or other signs of under-dosing.

The differences in bioavailability of Zubsolv® compared to Suboxone® tablet requires that different tablet strengths be given to the patient.

One Zubsolv® 5.7/1.4 mg sublingual tablet provides equivalent buprenorphine exposure to one Suboxone® 8/2 mg sublingual tablet.

When switching between Suboxone® dosage strengths and Zubsolv® dosage strengths the corresponding dosage strengths are:

Suboxone® sublingual tablets (including generic equivalents)	Corresponding dosage strength of Zubsolv® sublingual tablets
One 2 mg/0.5 mg buprenorphine/naloxone sublingual tablet	One 1.4 mg/0.36 mg Zubsolv® sublingual tablet
One 8 mg/2 mg buprenorphine/naloxone sublingual tablet	One 5.7 mg/1.4 mg Zubsolv® sublingual tablet
12 mg/3 mg buprenorphine/naloxone, taken as:	One 8.6 mg/2.1 mg Zubsolv® sublingual tablet
• One 8 mg/2 mg sublingual buprenorphine/naloxone tablet AND	
• Two 2 mg/0.5 mg sublingual buprenorphine/naloxone tablets	
16 mg/4 mg buprenorphine/naloxone, taken as:	One 11.4 mg/2.9 mg Zubsolv® sublingual tablet
• Two 8 mg/2 mg sublingual buprenorphine/naloxone tablets	

Appendix III: Guideline Committee Member Relationships with Industry and Other Entities

Guideline Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational or other financial benefit	Salary	Expert Witness	Other
Sandra D. Comer, PhD	Columbia University and NYSPI	• J&J	None	None	• Reckitt Benckiser**	None	None	None	None
	New York, NY	• AstraZeneca			• Omeras**				
	Professor of Neurobiology	Salix			• Medicinova**				
		• Cauarus							
		• Pfizer							
		• Mallincrodt							
Chinazo Cunningham, MD, MS	Albert Einstein College of Medicine, Yeshiva University	None	None	None	None	None	None	None	Quest Diagnostics**
	Bronx, NY								
Marc Fishman, MD, FASAM	Maryland Treatment Centers	• CRC Health Group, Advisory Board	None	Maryland Treatment Centers**	• Alkermes	None	Maryland Treatment Centers**	Board of Physician case reviews	None
	Baltimore, MD	• NY State JBS/SAMHSA Youth Opioid Addiction Project			• US World Meds**				
	Medical Director	• University of Maryland			• NIDA**				
Adam Gordon, MD, MPH, FASAM	University of Pittsburgh and VA Pittsburgh Healthcare System	None	None	None	None	None	None	None	None
Kyle Kampman, MD, TRI (Chair and Principal Investigator)	University of Pennsylvania	None	None	None	Braeburn Pharma	None	None	None	None
	VAMC								
	Philadelphia, PA								
	Professor of Psychiatry/Staff Physician								
Daniel Langleben, MD	University of Pennsylvania	None	None	None	Alkermes	None	None	None	None
	Philadelphia, PA								
	Associate Professor								
Benjamin Nordstrom, MD, PhD	Dartmouth College	None	None	None	None	None	None	None	None
	Hanover, NH								
	Associate Professor of Psychiatry								
	Director of Addiction Services								
	Director, Addiction Psychiatry Fellowship								

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Guideline Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational or other financial benefit	Salary	Expert Witness	Other
David Oslin, MD	University of Pennsylvania Medical Center	None	None	None	Department of Veteran Affairs, State of Pennsylvania	None	None	None	None
	Philadelphia, PA								
	Associate Professor of Psychiatry								
	Associate Chief of Staff, Behavioral Health								
George Woody, MD	Perelman School of Medicine	RADARS Scientific Advisory Board**	None	None	● Alkermes**	None	NIDA **	● U.S. Attorney's Office and DEA, Philadelphia**	None
	University of Pennsylvania				● Reckitt Benckiser**			● Pennsylvania Bureau of Professional and Occupational Affairs**	
	Philadelphia, PA				● Fidelity Capital**				
	Professor, Department of Psychiatry								
Tricia E. Wright, MD, MS	University of Hawaii	None	None	None	None	None	None	None	None
	John A. Burns School of Medicine								
	Honolulu, HI								
	Assistant Professor								
Stephen A. Wyatt, D.O.	Carolinas Healthcare System	None	None	None	None	None	None	None	None
	Medical Director, Addiction Medicine								
	Charlotte, NC								

The above table presents the relationships of Guideline Committee Members during the past 12 months with industry and other entities that were determined to be relevant to this document. These relationships are current as of the completion of this document and may not necessarily reflect relationships at the time of this document's publication. A person is deemed to have a *significant* interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of $10,000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be *modest* if it is less than *significant* under the preceding definition. *No financial relationship* pertains to relationships for which there is no monetary reimbursement.**Indicates significant relationship.

Appendix IV: ASAM Quality Improvement Council (Oversight Committee) Relationships with Industry and Other Entities

Oversight Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, organization, or Other Financial Benefit	Salary	Expert Witness	Other
John Femino, MD, FASAM	Meadows Edge Recovery Center	Inflexxion**	None	None	None	None	None	None	None
	North Kingstown, RI								
	Medical Director	Dominion Diagnostics**							
Margaret Jarvis, MD, FASAM, *Chair*	Marworth/Geisinger Health System	None	None	U.S. Preventive Medicine	None	None	Geisinger Health System**	Preston vs. Alpha Recovery Centers	Royalties-addiction article
	Waverly, PA								
	Medical Director of Marworth								
Margaret Kotz, DO, FASAM	University Hospitals of Cleveland	None	None	None	None	None	None	None	None
	Cleveland, OH								
	Case Medical Center								
	Medical Director, Addiction Recovery Services								
	Professor of Psychiatry and Anesthesiology								
	Case Western Reserve University School of Medicine								
Sandrine Pirard, MD, MPH, PhD	John Hopkins Bayview Medical Center	None	None	None	None	None	None	None	None
	Baltimore, MD								
	Psychiatrist								
Robert Roose, MD, MPH	Sisters of Providence Health System	None	None	None	None	None	None	None	None
	Holyoke, MA								
	CMO, Addiction Services								

The above table presents the relationships of the **ASAM Quality Improvement Council (Oversight Committee)** during the past 12 months with industry and other entities that were determined to be relevant to this document. These relationships are current as of the completion of this document and may not necessarily reflect relationships at the time of this document's publication. A person is deemed to have a *significant* interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of $10,000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be *modest* if it is less than *significant* under the preceding definition. *No financial relationship* pertains to relationships for which there is no monetary reimbursement.**Indicates significant relationship.

Appendix V: External Reviewer Relationships with Industry and Other Entities

External Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, organizational or other financial benefit	Salary	Expert Witness	Other
B. Steven Bentsen, MD, DFAPA	Value Options	Beacon Health Options	None	None	None	None	Beacon Health Options- Medical Director**	None	None	None
		Regional Chief Medical Officer								
Melinda Campopiano, MD	Substance Abuse Mental Health Services Administration (SAMHSA)	SAMHSA	None	None	None	None	None	None	None	None
		Medical Officer								
Timothy Cheney	Faces and Voices of Recovery (FAVOR)	Chooper's Guide	● FAVOR	None	None	None	None	None	None	None
		Managing Partner	● Floridians for Recovery							
			● Maine Harm Reduction Coalition							
			● C4 Recovery Solutions**							
H. Westley Clark, MD	Individual Reviewer	Santa Clara University	None	None	None	None	None	None	None	None
		Dean's Executive Professor, Public Health Program								
Kelly Clark, MD, MBA, FASAM, DFAPA	Individual Reviewer- ASAM Board Member	Clean Slate Addiction Treatment Centers	● Grunenthal US	None	● CVS Caremark	None	None	BHG**	None	None
			● Behavioral Health Group (BHG)**		● Clean Slate**			Clean Slate **		
			● Clean Slate**							
Itai Danovitch, MD	Individual Reviewer– ASAM State Chapter Leader	Cedars-Sinai Medical Center	None	None	None	None	None	None	None	None
		Chairman, Dept of Psychiatry								
Karen Drexler, M.D.	U.S. Department of Veterans Affairs	Department of Veterans Affairs	None	None	None	None	None	None	None	None
		Deputy National Program Director- Addictive Disorders								
Michael Fingerhood, MD	Individual Reviewer	John Hopkins University	None	None	None	None	None	None	None	None
		Associate Professor of Medicine								
Kevin Fiscella, MD, MPH	National Commission on Correctional Health Care (NCCHC)	University of Rochester	None	None	None	None	None	None	None	None
		Professor, Family Medicine, Public Health Science								
Rollin M. Gallagher, MD, MPH	Individual Reviewer	Philadelphia VA Medical Center	None	None	None	None	None	None	None	None
		National Program Director for Pain Management								
D. Ray Gaskin Jr., MD FASAM	Individual Reviewer- Georgia Chapter President	Self-employed	None	● Reckitt Benckiser	None	None	None	None	None	None
		Physician		● Orexo						

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External Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, organizational or other financial benefit	Salary	Expert Witness	Other
Stuart Gitlow, MD, MPH, MBA, FAPA	Individual Reviewer-President, ASAM	Self-employed Physician	Orexo Medical Director (January-June 2014)**	None	None	None	None	None	None	None
Dennis E. Hagarty, MSN, RN, CARN-AP, LCAS	International Nurses Society on Addiction (IntNSA)	Charles George VAMC	None	None	None	None	None	None	None	None
Henrick J. Harwood	National Association of State Alcohol and Drug Abuse Directors, Inc. (NASADAD)	NASADAD Deputy Executive Director	None	None	None	None	None	None	None	None
Frank P. James, MD JD	Optum/UBH	United HealthCare Associate Medical Director	None	None	None	None	None	None	None	None
Hendree Jones, MD	Individual Reviewer	University of North Carolina Executive Director/Professor OB/GYN	None	None	None	None	None	None	None	None
Miriam Komaromy, MD	Individual Reviewer	University of New Mexico, Echo Institute Associate Director, Echo Institute	None	None	None	None	None	None	None	None
Mark L. Kraus, M.D., FASAM, DABAM	Individual Reviewer-ASAM Board Member	Franklin Medical Group, PC Asst. Clinical Professor of Medicine, Yale University School of Medicine; Chief Medical Officer, Connecticut Counseling Centers	● BioDelivery Services, International; ● Indivior/ Reckitt Benckiser; ● PCM Healthcare	● Biodelivery Services International; ● Indivior/Reckitt Benckiser; ● PCM HealthcareASAM; Coalition on Physician Education on Substance Use Disorders	None	None	None	None	Defendant physician on regarding proper scope of practice	None
Joshua D. Lee, MD MSc	Individual Reviewer	NYU School of Medicine Associate Professor/Physician	None	None	None	Alkermes; Reckitt Benckiser**	None	None	None	None
David Mee-Lee, MD	Individual Reviewer	The Change Companies Senior Vice-President	None	None	None	None	None	None	None	None
Frances R. Levin, MD	American Psychiatric Association (APA)—Council on Addiction Psychiatry	Columbia University Kennedy Leavy Professor of Psychiatry at CUMC	GW Pharmaceuticals	None	None	US World Med	None	None	None	None
Petros Levounis, MD	Individual Reviewer	Rutgers NJ Medical School Chair, Department of Psychiatry	None	None	None	None	None	None	None	None
Sharon Levy, MD	American Academy of Pediatrics (AAP)	Boston Children's Hospital Director, Adolescent Substance Abuse Program	None	None	None	None	None	None	None	None

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External Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, organizational or other financial benefit	Salary	Expert Witness	Other
Michelle Lofwall, MD	Individual Reviewer-Past President, ASAM Kentucky Chapter	University of Kentucky Associate Professor, Behavioral Science and Psychiatry	• PCM Scientific (Reckitt Benckiser) • CVS Caremark	None	None	Braeburn Pharmaceuti-cals	None	None	None	None
Ed Madalis, LPC	Geisinger Health Plan	Geisinger Health Plan Lead Behavioral Health Coordinator	None	None	None	None	None	None	None	None
Steven C. Matson, MD	Individual Reviewer— ASAM Ohio Chapter President	Nationwide Children's Hospital Chief, Division of Adolescent Medicine, Associate Professor of Pediatrics	None	None	None	None	None	None	None	None
Michael Miller, MD, FASAM, FAPA	Individual Reviewer	Medical Director Herrington Recovery Center	Curry Rockefeller Group	• Alkermes • BDSI	None	None	• Braeburn Pharma • BDSI	None	None	None
Ivan Montoya	National Institute for Drug Abuse (NIDA)	NIDA Deputy Director, DPMC	None	None	None	None	None	None	None	None
Douglas Nemecek, MD, MBA	CIGNA	CIGNA Chief Medical Officer-Behavioral Health	None	None	None	None	None	None	None	None
Yngvild Olsen, MD	Individual Reviewer— ASAM Maryland Chapter President	Institutes for Behavior Resources, Inc. Medical Director	None	CORE REMS	None	Friends Research Institute	None	Institutes for Behavior Resources, Inc.**	None	None
David Pating, MD	Individual Reviewer	Permanente Medical Group Chief, Addiction Medicine, Kaiser SFO	None	None	None	None	None	None	None	None
Ashwin A. Patkar, MD	Individual Reviewer	Duke University Medical Center Professor of Psychiatry and Community and Family Medicine	• Reckitt Benckiser • BDSI • Cubist • Titan Pharma • Braeburn Pharm	BDSI, Alkermes	Generys Biopharma	• PI Forest Research Institute • Co-I NIDA and SAMHSA grants • PI Titan Pharma–ceuticals **	None	None	None	None
Jeffrey Quamme, MD	Individual Reviewer	Connecticut Certification Board Executive Director	None	None	None	None	None	None	None	None

(Continued)

External Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, organizational or other financial benefit	Salary	Expert Witness	Other
John A. Renner, Jr., MD	American Psychiatric Association (APA)—Council on Addiction Psychiatry	VA Boston Healthcare System; Associate Chief of Psychiatry	National Institute on Drug Abuse, Clinical Trials Network	None	None	None	• Depart-ment of Psychiatry Boston University Center • Psychiatric Assoc, Consultant and Council on Addiction Psychiatry • Academy of Addiction Psychiatry Consultant & Board of Trustees	VA Boston Healthcare System**	None	None
Robert L. Rich, Jr. MD, FAAFP	American Academy of Family Physicians (AAFP)	Community Care of the Lower Cape Fear; Medical Director/Reviewer	None	None	None	None	None	Community Care of the Lower Cape Fear	None	None
A. Kenison Roy III, MD	Individual Reviewer-ASAM Board Member	Biobehavioral Medicine Company, LLC; Owner/Medical Director	Orexo, Biobehavioral Sciences, Inc. (BDSI)	• Orexo, • BDSI, • Alkermes	Addiction Recovery Resources, Inc.**	None	None	None	None	None
Albert A. Rundio, Jr. PhD	International Nurses Society on Addictions (IntNSA)	Drexel University; Associate Dean for Post-Licensure Nursing Programs and CNE	None	None	None	None	None	None	None	None
Edwin Salsitz, M.D.	Individual Reviewer	Mount Sinai Beth Israel; Physician	None	None	None	None	None	None	None	None
Andrew J. Saxon, MD	American Psychiatry Association (APA)—Council on Addiction Psychiatry	Department of Veterans Affairs; Director, Center of Excellence in Substance Abuse Treatment and Education	None	None	None	• NIDA CTN grant** • Alkermes • ReckittBen-cker	None	None	None	None
Ian A Shaffer, MD	Healthfirst	Executive Medical Director & VP	None	None	None	None	None	None	None	None
Dominique Simon	Allies in Recovery	Allies in Recovery; Director	None	None	None	None	None	None	None	None
Sandra Springer, MD	Individual Reviewer	Yale School of Medicine; Associate Professor of Medicine	None	None	None	NIH-funded research**	None	None	None	Free drug and placebo from Alker-mes

(**Continued**)

External Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, organizational or other financial benefit	Salary	Expert Witness	Other
Knox Todd, MD. MPH	American College of Emergency Physicians (ACEP)	MD Anderson Cancer Center	Kaleo, Inc.	None	None	None	Depomed, Inc.	None	None	None
		Professor and Chair of Emergency Medicine								
Howard Wetsman, MD	Individual Reviewer- ASAM Board Member	Self-employed	None	None	• Wetsman Forensic Medicine	None	None	None	None	None
		Chief Medical Officer			• KHM LLC dba Sagenex Labs					
					• Rush Medical					
					• Idea Breeder LLC,					
					• Tres Amigos LLC					
					• Keystone Acquisition LLC					
Amanda Wilson, MD	Individual Reviewer	Clean Slate Addiction Treatment Centers	None	None	Clean Slate Centers, Inc. **	None	None	Clean Slate Centers, Inc.**	None	None
		President and CEO								
Celia Winchell	Food and Drug Administration (FDA)	Medical Team Leader	None	None	None	None	None	None	None	None
		Food and Drug Administration								

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