The ASAM National Practice Guideline 2020 Focused Update

The ASAM

NATIONAL PRACTICE GUIDELINE

For the Treatment of Opioid Use Disorder

2020 Focused Update

ASAM American Society of Addiction Medicine

Adopted by the ASAM Board of Directors December 18, 2019.

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Abbreviations and Acronyms

AA – Alcoholics Anonymous
ACOG – American College of Obstetrics and Gynecology
ACT – Assertive Community Treatment
AIDS – Acquired Immunodeficiency Syndrome
ASAM – American Society of Addiction Medicine
CBT – Cognitive Behavioral Therapy
CDC – Centers for Disease Control and Prevention
CNS – Central Nervous System
COWS – Clinical Opioid Withdrawal Scale
DATA 2000 – Drug Addiction Treatment Act of 2000
DEA – Drug Enforcement Agency
DSM-4 – 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 – U.S. 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 Absence Syndrome
NIH – National Institutes of Health
NIDA – National Institute on Drug Abuse
NIAAA – National Institute on Alcohol Abuse and Alcoholism
NOWS – Neonatal Opioid Withdrawal 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 Controlled 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 – Ultra-rapid 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 substance use, gambling, video gaming, or compulsive sexual behaviors.[1] Use of FDA approved medications for the treatment of substance use disorder is consistent with abstinence.

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 previously applied to one category of psychoactive substance-related disorders in the DSM. While recognizing that the term 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.

Addiction: Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences. Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic diseases.

Addiction specialist clinician: A health professional involved in the assessment, diagnosis, and treatment of addiction, such as a physician, psychologist, nurse practitioners (NPs), physician assistants (PA), clinical nurse specialists, certified registered nurse anesthetists, certified nurse midwives (as distinguished from one specializing in research).

Addiction specialist physician: Addiction specialist physicians include addiction medicine physicians and addiction psychiatrists who hold either a subspecialty board certification in addiction medicine from the American Board of Preventive Medicine, 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 ASAM.

Adherence (see also compliance): 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 may be narrowly applied to how well patients follow medication instructions or, 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.

Adolescence: The American Academy of Pediatrics categorizes adolescence as the totality of three developmental stages (early-, middle- and late-adolescence)—puberty to adulthood—that occur generally between 11 and 21 years of age.[1] This clinically-driven definition may differ from legal definitions.

Agonist medication: See Opioid Agonist Medication.

Antagonist medication: See Opioid Antagonist Medication.

ASAM Criteria dimensions: The ASAM Criteria use six dimensions to define a holistic biopsychosocial assessment of an individual to be used for service and treatment planning including: acute intoxication or withdrawal potential; biomedical conditions and complications; emotional, behavioral, or cognitive conditions or complications; readiness for change; continued use or continued problem potential; and recovery/living environment.[2]

Assertive community treatment (ACT): An evidence-based, outreach-oriented, service delivery model for people with severe and persistent mental illness(es) that uses a team-based model to provide comprehensive and flexible treatment.

Clinician: A health professional involved in the assessment, diagnosis, and treatment of medical problems, such as a physician, psychologist, nurse practitioners (NPs), physician assistants (PA), clinical nurse specialists, certified registered nurse anesthetists, certified nurse midwives (as distinguished from one specializing in research).

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 substances.

Co-occurring disorders: Concurrent substance use and physical or mental disorders. Other terms used to describe co-occurring disorders include dual diagnosis, dual disorders, 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.

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.

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

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

Criminal Justice System: Consists of law enforcement agencies, courts and accompanying prosecution and defense lawyers, and agencies for detaining and supervising offenders. The total correctional population is the population of persons incarcerated, either in a prison or a jail, and persons supervised in the community, either through problem solving courts or on probation or parole.

Dependence: Used in three different ways: physical dependence is a state of neurological 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.[3]

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 substance use and addiction-related problems, especially medical complications and transmission of infectious diseases, without necessarily requiring abstinence. A range of treatment and recovery support activities may be included in a harm reduction strategy.

Initiation (office and home): The phase of opioid use disorder treatment during which medication dosage levels are adjusted until a patient attains stabilization. Buprenorphine initiation may take place in an office-based setting or home-based setting. By regulation, methadone initiation must take place in an OTP or acute care setting (under limited circumstances).[4,5] The previous version of these guidelines used the term induction. While the meaning is the same in this context, the Guideline Committee noted that this language did not align with the terminology used for other medical conditions and can make the process sound more difficult and complex than it is.

Illicit opioid use (including nonmedical use): Use of an illicit opioid or the use of a prescribed medicine for reasons other than those intended by the prescriber, for example, to produce positive 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).

Maintenance medication(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 medications for 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 medications for addiction are also designed to mitigate against the risk of overdose. Depending on the circumstances of a given case, maintenance medications can be temporary or can remain in place lifelong. Integration of pharmacotherapy with psychosocial treatment generally is associated with the best clinical results. Maintenance medications can be part of an individual's treatment plan in abstinence-based recovery activities or can be a part of harm reduction strategies.

Medication management: Services that focus on the appropriateness, effectiveness, and safety of medications for a given patient. These services include monitoring and evaluating the patient's response to medication (including ongoing misuse of substances); dose titration as clinically indicated; education to ensure the patient understands their treatment plan, how to take their medications, potential side effects, and the importance of adherence; and provision of recommendations for other treatment and recovery support services as indicated. These services are intended to promote ongoing engagement in treatment, optimize the patient's medication response, and prevent relapse.

Moderation management: Moderation management 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.

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.

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 naltrexone pharmacotherapy.

Naltrexone-facilitated opioid withdrawal management: This is a method of withdrawal management that involves the use of multiple small doses of naltrexone, sometimes in combination with buprenorphine, over several days to manage withdrawal and facilitate the initiation of treatment with naltrexone.[4]

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.

Neuroadaptation: See Tolerance for the definition.

Office-based opioid treatment (OBOT): Clinicians in private practices or several types of public sector clinics that can be authorized to prescribe the partial opioid agonist buprenorphine in outpatient settings. There is no regulation, *per se*, of the clinic site itself, but of the individual clinician who prescribes buprenorphine.

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.

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.

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

Opioid antagonist medication: Opioid antagonist medications pharmacologically occupy opioid receptors, but do not activate the receptors. This effectively blocks the receptor, preventing the brain from responding to other opioids. The result is that further use of opioids does not produce analgesia, euphoria or intoxication.[1]

Opioid intoxication: A condition that may follow 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.

Opioid treatment program (OTP): A program certified by the United States, Substance Abuse and Mental Health Services Administration (SAMHSA), to treat patients with opioid use disorder using methadone. There programs may also offer treatment with buprenorphine and/or naltrexone. An OTP can exist in several 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.

Opioid treatment services: An umbrella term that encompass 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.

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

Opioid withdrawal management: Usually used to refer to a process of withdrawing a person from a specific psychoactive substance in a safe and effective manner. The term encompasses safe management of intoxication states (more literally, detoxification) and of withdrawal states. In this document, the term detoxification has been replaced by the term withdrawal management.[2]

Opioid withdrawal: Over time, opioids 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.

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, that results in a serious toxic reaction or death.

Patient: As used in this document, an individual receiving substance use disorder treatment. The terms client and patient sometimes are used interchangeably, although staff in nonmedical settings more commonly refer to clients.

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.

Psychosocial interventions: Nonpharmacological interventions that may include structured, professionally administered interventions (e.g., cognitive behavior therapy or insight-oriented psychotherapy) or nonprofessional interventions (e.g., self-help groups and non-pharmacological interventions from traditional healers).

Psychosocial treatment: Any nonpharmacological, professionally administered interventions (e.g., cognitive behavior therapy or insight-oriented psychotherapy) carried out in a therapeutic context at an individual, family, or group level.

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

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.)

Remission: A state associated with an abatement of signs and symptoms that characterize active addiction. Many individuals in a remission state remain actively engaged in the process of recovery. Reduction in signs or symptoms constitutes improvement in a disease state, but remission involves a return to a level of functioning that is free of active symptoms and/or is marked by stability in the chronic signs and symptoms that characterize active addiction.

Relapse: A process in which an individual who has established disease remission 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 substances or re-engaging in addictive behaviors is the latter part of the process, which can be prevented by early intervention.

Sedative, hypnotic, or anxiolytics: This class of substances includes all prescription sleeping medications and most prescription antianxiety medications (e.g. benzodiazepines, Z-medications, and gabapentinoids). Nonbenzodiazepine antianxiety medications, such as buspirone and gepirone, are not included in this class because they are not associated with significant misuse.

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.

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

Stabilization: Attainment of a medically stable, steady state in which the patient is adequately supported to prevent deterioration of their illness.

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, nicotine, and/or other drugs despite significant related problems. Diagnostic criteria are given in the DSM-5.[5] Substance use disorder is the new nomenclature for what was included as substance dependence and substance abuse in the DSM-4.[6]

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.

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

EXECUTIVE SUMMARY

Purpose

The American Society of Addiction Medicine (ASAM) developed this *National Practice Guideline for the Treatment of Opioid Use Disorder* 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*.) This guideline is an update and replacement of the 2015 ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use.[7]

Background Updated

Opioid use disorder is a brain disorder that can range in severity from mild to severe. Diagnosis of this disorder is based on a checklist of symptoms defined in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5) developed by the American Psychiatric Association.[5]

ASAM defines addiction as "a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences." Addiction is a serious biopsychosocial illness, meaning that biological, psychological, and social factors can all contribute to both the development of, and recovery from, this disease. *The ASAM Criteria* (discussed in Part 1) provide a framework for assessing how diverse biopsychosocial factors contribute to an individual patient's addiction and the type and intensity of treatment needed to support their recovery.[2] ASAM views addiction as fundamentally a neurological disease involving 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. In this context, the preferred term by ASAM for this disorder is addiction involving opioid use.

A variety of substances commonly associated with addiction work on specific receptors and neurotransmitter systems in the nervous system. Pharmacological agents used in the treatment of addiction exert their effects via actions on specific receptors. Hence, the medications used in the treatment of addiction have efficacy based on their own molecular structure and the particular neurotransmitter receptors 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 U.S. Food and Drug Administration (FDA) for the treatment of opioid dependence (using DSM, 4th Edition [DSM-4] terminology), is also FDA-approved for the treatment of alcohol dependence (DSM-4).[6]

ASAM encourages clinicians, researchers, educators, and policy makers to use the term "addiction involving " 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. However, 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.

In 2018, an estimated 10.3 million people in the United States misused opioids (representing 3.7% of the population aged 12 or older), including 9.9 million people who misused pain relievers, and 808,000 who misused heroin.[8] The 2018 National Survey of Drug Use and Health (NSDUH) further found that 2.0 million persons in America met DSM-4 criteria for opioid use disorder.[8]

Opioid misuse is associated with increased morbidity and mortality. The leading causes of death in people using opioids for non-medical purposes are overdose and trauma.[9] Injection drug use (intravenous or intramuscular [IM]) increases the risk of being exposed to HIV, viral hepatitis, and other infectious agents. As a result of the opioid epidemic, drug-use associated infections, including infective endocarditis, osteomyelitis, septic arthritis, and epidural abscesses, are increasing. A statewide study in North Carolina found that drug-use associated infective endocarditis requiring hospitalization and valve surgeries increased more than 12-fold between 2007 and 2017.[10]

Scope of Guideline

This Practice Guideline was developed for the treatment of opioid use disorder and the prevention of opioid overdose related deaths. The medications covered in this guideline are mainly, but not exclusively, those that have been FDA-approved for the treatment of opioid dependence (DSM-4) or opioid use disorder (DSM-5).[5,6] The most recent version, 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-4 and opioid use disorder from DSM-5, optimal concordance occurred when four or more DSM-5 criteria were endorsed (i.e., the DSM-5 threshold for moderate opioid use disorder).[11] 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, whether 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. The recommendations in this guideline reflect the consensus of an independent committee (see Methodology Section) convened by ASAM between September 2018 and November 2019, to oversee a focused update of this Practice Guideline. This Practice Guideline will be updated regularly as clinical and scientific knowledge advances.

Prescribed courses of treatment described 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.

ASAM recognizes that there are challenges to implementation of these guidelines in certain settings, particularly in relation to the availability of all FDA approved medications for the treatment of opioid use disorder and access to psychosocial treatment in various communities and settings. However, this guideline aims to set the standard for best clinical practice, providing recommendations for the appropriate care of all patients with opioid use disorder in diverse settings. 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. 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.[12] 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. For the 2015 guideline development process, ASAM's then Quality Improvement Council, chaired by Margaret Jarvis, MD, oversaw the selection process for the independent development committee, referred to as the Guideline Committee.[7]

The 2015 Guideline Committee was comprised of 11 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 2015 Guideline Committee was assisted by a technical team of researchers from the Treatment Research Institute (TRI) affiliated with the University of Pennsylvania and worked under the guidance of Dr. Kyle Kampman who led the TRI team as Principal Investigator in implementing the RAM.

2019 Focused Update New

Between September 2018 and November 2019, ASAM reconvened an independent committee (see Methodology Section) to oversee a focused update of this Practice Guideline.[7] The purpose of the focused update was to develop new and revised recommendations based on a targeted review of new evidence, FDA approval of new buprenorphine formulations (see Table 1) and evolving clinical practice guidance. A full update of the guideline is scheduled to begin in 2021. ASAM's Quality Improvement Council worked with a technical team from RTI International to develop and oversee the scope of work for the focused update.

The methods used to search the literature and subsequently develop guideline statements were consistent with the RAM methodology employed for the 2015 publication. Criteria for inclusion in the focused update included new evidence and guidelines that were considered a) clinically meaningful and applicable to a broad range of clinicians treating addiction involving opioid use, and b) urgently needed to ensure the guideline reflects the current state of the science for the existing recommendations, aligns with other relevant practice guidelines, and reflects newly approved medications and formulations. Relevant evidence and current practices not meeting these criteria will be reviewed and incorporated into the full update as appropriate.

TABLE 1. Buprenorphine Formulations

Generic Name	Route of Administration Dosing	Brand Names	For the Treatment of	Formulation Considerations
Buprenorphine (monoproduct)	Sublingual Tablets Daily	Generic versions available similar to Subutex	Opioid withdrawal and opioid use disorder	Some risk for diversion or misuse; Requires daily compliance
Buprenorphine and naloxone	Sublingual tablets and film Daily	Generic versions available in addition to Suboxone, Cassipa, Zubsolv, Bunavail	Opioid withdrawal and opioid use disorder	Lower potential for misuse and diversion (compared to monoproduct); Requires daily compliance
Buprenorphine extended-release	Extended-release Injection (Monthly)	Sublocade	Moderate to severe opioid use disorder in patients who have initiated treatment with transmucosal buprenorphine followed by dose adjustment for a minimum of 7 days	No risk for patient diversion or misuse; Requires patients to be on a stable dose of transmucosal buprenorphine for at least 7 days; Monthly instead of daily medication compliance; Less fluctuation in buprenorphine levels (compared to daily doses)
Buprenorphine extended-release	Extended-release Injection (Weekly or Monthly)	Brixadi	Moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of transmucosal buprenorphine or who are already being treated with buprenorphine	Tentative approval from FDA (not eligible for marketing in the U.S. until November 30, 2020). No risk for patient diversion or misuse; only a single prior dose of transmucosal buprenorphine required prior to initiation; Weekly or Monthly instead of daily medication compliance; Less fluctuation in buprenorphine levels (compared to daily doses)
Buprenorphine hydrochloride	Subcutaneous Implant (Every 6 months)	Probuphine Implant	Treatment of opioid use disorder in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine (i.e., no more than 8 mg per day)	Requires prolonged stability on 8 mg per day or less transmucosal buprenorphine; No risk for patient diversion or misuse; Healthcare provider training required for implant insertion and removal; Insertion site should be examined one week after insertion; Implant must be removed after 6 months; Risks associated with improper insertion and removal; Currently only FDA approved for a total treatment duration of one year (one insertion per arm); Less fluctuation in buprenorphine levels (compared to daily doses)

Some patients may experience withdrawal/cravings when switched to a different formulation.
Subutex was discontinued.
Table content was derived from FDA labels. Labels and label updates can be accessed at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

Summary of Recommendations

Part 1: Assessment and Diagnosis of Opioid Use Disorder

Assessment Recommendations

1. The 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. NEW Comprehensive assessment of the patient is critical for treatment planning. However, completion of all assessments should not delay or preclude initiating pharmacotherapy for opioid use disorder. If not completed before initiating treatment, assessments should be completed soon thereafter.
3. MINOR REVISION Completion of the patient's medical history should include screening for concomitant medical conditions, including psychiatric disorders, infectious diseases (viral hepatitis, HIV, and tuberculosis [TB]), acute trauma, and pregnancy.
4. MINOR REVISION 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) should ensure that a current physical examination is contained within the patient medical record before (or soon after) a patient is started on pharmacotherapy.
5. MINOR REVISION Initial laboratory testing should include a complete blood count, liver enzyme tests, and tests for TB, hepatitis B and C, and HIV. Testing for sexually transmitted infections should be strongly considered. Hepatitis A and B vaccinations should be offered, if appropriate.
6. MINOR REVISION Women of childbearing potential should be tested for pregnancy, and all women of childbearing potential should be queried regarding methods of contraception.
7. MINOR REVISION Patients being evaluated for opioid use disorder, 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 (such as is outlined in *The ASAM Criteria* and *The ASAM Standards*).[12,13]
8. MINOR REVISION Opioid use disorder is often co-occurring with other substance use disorders. Evaluation of a patient with opioid use disorder should include a detailed history of other past and current substance use and substance use disorders.
9. MINOR REVISION The use of cannabis, stimulants, alcohol, and/or other addictive drugs should not be a reason to withhold or suspend opioid use disorder treatment. However, patients who are actively using substances during opioid use disorder treatment may require greater support including a more intensive level of care (see *The ASAM Criteria* and *The ASAM Standards*).[12,13]
10. MAJOR REVISION The use of benzodiazepines and other sedative-hypnotics should not be a reason to withhold or suspend treatment with methadone or buprenorphine. While the combined use of these medications increases the risk of serious side effects, the harm caused by untreated opioid use disorder can outweigh these risks. A risk-benefit analysis should be conducted, and greater support should be provided including careful medication management to reduce risks.[14]
11. MINOR REVISION A nicotine use query should be completed routinely for all patients and counseling on cessation of the use of tobacco products and electronic nicotine delivery devices (e.g. vaping) provided if indicated.
12. MINOR REVISION As part of comprehensive care the patient should receive a multidimensional assessment (as described in *The ASAM Criteria*), including an assessment of social and environmental factors to identify facilitators and barriers to addiction treatment and long-term recovery (including pharmacotherapy).[1] Addiction is a complex biopsychosocial illness, for which the use of medication(s) is only one component of comprehensive treatment.

Diagnosis Recommendations

1. MINOR REVISION Other clinicians may diagnose opioid use disorder, but confirmation of the diagnosis must be obtained by the prescriber 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. MINOR REVISION Validated clinical scales that measure withdrawal symptoms may be used to assist in the evaluation of patients with opioid use disorder.
4. MINOR REVISION Drug testing is recommended during the comprehensive assessment process, and during treatment to monitor patients for adherence to prescribed medications and use of alcohol, illicit, and controlled substances. The frequency of testing is determined by several factors including stability of the patient, type of treatment, and treatment setting. For additional information see The ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine guidance document.[15]

Part 2: Treatment Options

1. MAJOR REVISION All FDA approved medications for the treatment of opioid use disorder should be available to all patients. Clinicians should consider the patient's preferences, past treatment history, current state of illness, and treatment setting when deciding between the use of methadone, buprenorphine, and naltrexone.
2. NEW There is no recommended time limit for pharmacological treatment.
3. MAJOR REVISION Patients' psychosocial needs should be assessed, and patients should be offered or referred to psychosocial treatment based on their individual needs. However, a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacotherapy, with appropriate medication management. Motivational interviewing or enhancement can be used to

encourage patients to engage in psychosocial treatment services appropriate for addressing individual needs.

4. MINOR REVISION The venue in which treatment is provided should be carefully considered. Methadone can only be provided in opioid treatment programs (OTPs) and acute care settings (under limited circumstances). Buprenorphine can be prescribed by waivered clinicians in any setting, including OTPs and office based opioid treatment (OBOT) in accordance with the Federal law (21 CFR §1301.28). Naltrexone can be prescribed in any setting by any clinician with the authority to prescribe medication. Clinicians should consider a patient's psychosocial situation, co-occurring disorders, and risk of diversion when determining which treatment setting is most appropriate (see *The ASAM Criteria* for additional guidance[1]).
5. MINOR REVISION Patients with active co-occurring alcohol use disorder or sedative, hypnotic, or anxiolytic use disorder (or who are in treatment for a substance use disorder involving use of alcohol or other sedative drugs, including benzodiazepines or benzodiazepine receptor agonists) may need a more intensive level of care than can be provided in an office-based setting. Persons who are regularly using alcohol or other sedatives, but do not meet the criteria for diagnosis of a specific substance use disorder related to that class of drugs, should be carefully monitored.
6. MAJOR REVISION The prescribing of benzodiazepines or other sedative-hypnotics should be used with caution in patients who are prescribed methadone or buprenorphine for the treatment of an opioid use disorder. While the combined use of these drugs increases the risk of serious side effects, the harm caused by untreated opioid use disorder can outweigh these risks. A risk-benefit analysis should be conducted when deciding whether to co-prescribe these medications.
7. 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.
8. NEW Opioid dosing guidelines developed for chronic pain, expressed in morphine milligram equivalents (MME), are not applicable to medications for the treatment of opioid use disorders.
9. MINOR REVISION Oral naltrexone for the treatment of opioid use disorder is often adversely affected by poor medication adherence and should not be used except under very limited circumstances. 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.
10. MINOR REVISION The Prescription Drug Monitoring Program (PDMP) should be checked regularly for the purpose of confirming medication adherence and to monitor for the prescribing of other controlled substances.
11. NEW Naloxone, for the reversal of opioid overdose, should be provided to patients being treated for, or with a history of, opioid use disorder. Patients and family members/significant others should be trained in the use of naloxone in overdose.

Part 3: Treating Opioid Withdrawal

1. MINOR REVISION Using methadone or buprenorphine for opioid withdrawal management is recommended over abrupt cessation of opioids. Abrupt cessation of opioids may lead to strong cravings, and/or acute withdrawal syndrome which can put the patient at risk for relapse, overdose, and overdose death.
2. MINOR REVISION Opioid withdrawal management (i.e. detoxification) on its own, without ongoing treatment for opioid use disorder, is not a treatment method for opioid use disorder and is not recommended. Patients should be advised about the risk of relapse and other safety concerns, including increased risk of overdose and overdose death. Ongoing maintenance medication, in combination with psychosocial treatment appropriate for the patient's needs, is the standard of care for treating opioid use disorder.
3. MINOR REVISION 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. MINOR REVISION By regulation, opioid withdrawal management with methadone must be done in an OTP or an acute care setting (under limited circumstances). For patients withdrawing from short acting opioids the initial dose should typically be 20-30 mg per day and the patient may be tapered off in approximately 6-10 days.
5. MAJOR REVISION Opioid withdrawal management with buprenorphine should not be initiated until there are objective signs of opioid withdrawal. (See Part 3 for more information on the timing of initiating buprenorphine.) Once signs of withdrawal have been objectively confirmed, a dose of buprenorphine sufficient to suppress withdrawal symptoms is given (an initial dose of 2-4 mg titrated up as needed to suppress withdrawal symptoms).
6. MAJOR REVISION Alpha-2 adrenergic agonists (e.g., FDA-approved lofexidine and off-label clonidine) are safe and effective for management of opioid withdrawal. However, methadone and buprenorphine are more effective in reducing the symptoms of opioid withdrawal, in retaining patients in withdrawal management, and in supporting the completion of withdrawal management.
7. Opioid withdrawal management using ultra-rapid opioid detoxification (UROD) is not recommended due to high risk for adverse events or death. Naltrexone-facilitated opioid withdrawal management can be safe and effective but should be used only by clinicians experienced with this clinical method, and in cases in which anesthesia or conscious sedation are not employed.

Part 4: Methadone

1. MINOR REVISION Methadone is a recommended treatment for patients with opioid use disorder, who are able to give informed consent and have no specific contraindication for this treatment.

2. MAJOR REVISION The recommended initial dose of methadone ranges from 10 to 30 mg, with reassessment as clinically indicated (typically in 2 to 4 hours). Use a lower-than-usual initial dose (2.5 to 10 mg) in individuals with no or low opioid tolerance.
3. MAJOR REVISION Following initial withdrawal stabilization, the usual daily dose of methadone ranges from 60 to 120 mg. Some patients may respond to lower doses and some may need higher doses. Methadone titration should be individualized based on careful assessment of the patient's response and generally should not be increased every day. Typically, methadone can be increased by no more than 10 mg approximately every 5 days based on the patient's symptoms of opioid withdrawal or sedation.
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 prescribing non-monitored doses is appropriate.
5. MAJOR REVISION Patients' psychosocial needs should be assessed, and patients should be offered or referred to psychosocial treatment based on their individual needs, in conjunction with methadone in the treatment of opioid use disorder. However, a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay treatment with methadone, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
6. MINOR REVISION For patients who previously received methadone for the treatment of opioid use disorder, methadone should be reinstituted immediately if relapse occurs or if an assessment determines that the risk of relapse is high (unless contraindicated). Re-initiation of methadone should follow the recommendations above regarding initial dose and titration.
7. MINOR REVISION Strategies directed at relapse prevention are an important part of addiction treatment and should be included in any plan of care for a patient receiving opioid use disorder treatment or ongoing monitoring of the status of their disorder.
8. MINOR REVISION Transitioning from methadone to another medication for the treatment of opioid use disorder may be appropriate if the patient experiences dangerous or intolerable side effects or is not successful in attaining or maintaining treatment goals through the use of methadone.
9. MINOR REVISION Patients transitioning from methadone to buprenorphine in the treatment of opioid use disorder should ideally be on low doses of methadone before making the transition. 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 transitioning medications.
10. MINOR REVISION Patients transitioning from methadone to 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. MINOR REVISION There is no recommended time limit for pharmacological treatment with methadone. Patients who discontinue methadone treatment should be made aware of the risks associated with opioid overdose, and especially the increased risk of overdose death if they return to illicit opioid use. Treatment alternatives including buprenorphine (see Part 5) and naltrexone (see Part 6), as well as opioid overdose prevention with naloxone (see part 13), should be discussed with any patient choosing to discontinue treatment.

Part 5: Buprenorphine

1. NEW Buprenorphine is a recommended treatment for patients with opioid use disorder, who are able to give informed consent and have no specific contraindication for this treatment.
2. MINOR REVISION For patients who are currently opioid dependent, buprenorphine should not be initiated until there are objective signs of opioid withdrawal to reduce the risk of precipitated withdrawal. (See discussion).
3. MAJOR REVISION Once objective signs of withdrawal are observed, initiation of buprenorphine should start with a dose of 2–4 mg. Dosages may be increased in increments of 2–8 mg.
4. MAJOR REVISION The setting for initiation of buprenorphine should be carefully considered. Both office-based and home-based initiation are considered safe and effective when starting buprenorphine treatment. Clinical judgement should be used to determine the most appropriate setting for a given patient and may include consideration of the patient's past experience with buprenorphine and assessment of their ability to manage initiation at home.
5. MAJOR REVISION Following initiation, buprenorphine dose should be titrated to alleviate symptoms. To be effective, buprenorphine dose should be sufficient to enable patients to discontinue illicit opioid use. Evidence suggests that 16 mg per day or more may be more effective than lower doses. There is limited evidence regarding the relative efficacy of doses higher than 24 mg per day, and the use of higher doses may increase the risk of diversion.[16]
6. NEW The FDA recently approved several new buprenorphine formulations for treatment of opioid use disorder (see Table 1). As data regarding the effectiveness of these products are currently limited, clinicians should use these products as indicated and be mindful of emerging evidence as it becomes available.
7. MAJOR REVISION Patients' psychosocial needs should be assessed, and patients should be offered or referred to psychosocial treatment based on their individual needs, in conjunction with buprenorphine in the treatment of opioid use disorder. However, a patient's decision to decline psychosocial treatment or the absence

of available psychosocial treatment should not preclude or delay buprenorphine treatment, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.

8. MINOR REVISION Clinicians should take steps to reduce the chance of buprenorphine diversion. Recommended strategies may include frequent office visits (e.g., weekly in early treatment); drug testing, including testing for buprenorphine and metabolites; and recall visits for medication counts. Refer to ASAM's Sample Diversion Control Policy for additional strategies to reduce the risk for diversion[16]
9. MINOR REVISION Drug testing should be used to monitor patients for adherence to buprenorphine and use of illicit and controlled substances. For additional guidance see The ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine[14]
10. MINOR REVISION Patients should be seen frequently at the beginning of treatment until they are determined to be stable.
11. When considering a transition from buprenorphine to naltrexone, providers should note that 7–14 days should typically 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.
12. MINOR REVISION When considering a transition from buprenorphine to methadone, there is no required time delay because the transition to a full mu-opioid agonist from a partial agonist does not typically result in an adverse reaction.
13. MINOR REVISION There is no recommended time limit for pharmacological treatment with buprenorphine. Patients who discontinue buprenorphine treatment should be made aware of the risks associated with opioid overdose, and especially the increased risk of death if they return to illicit opioid use. Treatment alternatives including methadone (see Part 4) and naltrexone (see Part 6), as well as opioid overdose prevention with naloxone (see part 13) should be discussed with any patient choosing to discontinue treatment.
14. MINOR REVISION 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.

Part 6: Naltrexone

1. MAJOR REVISION Extended-release injectable naltrexone is a recommended treatment for preventing relapse to opioid use disorder in patients who are no longer physically dependent on opioids, able to give informed consent, and have no contraindications for this treatment.
2. MAJOR REVISION Extended-release injectable naltrexone should generally be administered every 4 weeks by deep IM injection in the gluteal muscle at the set dosage of 380 mg per injection. Some patients, including those who metabolize naltrexone more rapidly, may benefit from dosing as frequently as every 3 weeks.
3. MAJOR REVISION Oral naltrexone is not recommended except under limited circumstances (see Part 6 for more details).
4. MAJOR REVISION Patients' psychosocial needs should be assessed, and patients should be offered or referred to psychosocial treatment based on their individual needs, in conjunction with extended-release naltrexone. A patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay naltrexone treatment, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
5. MINOR REVISION There is no recommended length of treatment with 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. MINOR REVISION Transitioning from naltrexone to methadone or buprenorphine should be planned, considered, and monitored. Transitioning from an antagonist such as naltrexone to a full agonist (methadone) or a partial agonist (buprenorphine) is generally less complicated than transitioning 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 transitioned from naltrexone to buprenorphine or methadone will not have physical dependence on opioids and thus the initial doses of methadone or buprenorphine should be low. Patients should not be transitioned until a significant amount of the naltrexone is no longer in their system, about 1 day for oral naltrexone or 28 days for extended-release injectable naltrexone.
7. MINOR REVISION Patients who discontinue naltrexone treatment should be made aware of the increased risks associated with opioid overdose, and especially the increased risk of overdose death, if they return to illicit opioid use. Treatment alternatives including methadone (see Part 4) and buprenorphine (see Part 5), as well as overdose prevention with naloxone (see part 13) should be discussed with any patient choosing to discontinue treatment.

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

1. MAJOR REVISION Patients' psychosocial needs should be assessed, and patients should be offered or referred to psychosocial treatment, based on their individual needs, in conjunction with any pharmacotherapy for the treatment of, or prevention of relapse to, opioid use disorder. However, a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment of opioid use disorder, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.

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.

Part 8: Special Populations: Pregnant Women

1. NEW 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. MINOR REVISION Treatment with methadone or buprenorphine is recommended and should be initiated as early as possible during pregnancy.
3. MAJOR REVISION Pregnant women who are physically dependent on opioids should receive treatment using methadone or buprenorphine rather than withdrawal management or psychosocial treatment alone.
4. MAJOR REVISION A medical examination and psychosocial assessment are recommended when evaluating pregnant women for opioid use disorder. However, completion of all assessments should not delay or preclude initiating pharmacotherapy for opioid use disorder. If not completed before initiating treatment, assessments should be completed as soon as possible thereafter.
5. Obstetricians and gynecologists, and other healthcare providers that care for pregnant women, 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.
6. MAJOR REVISION The psychosocial needs of pregnant women being treated for opioid use disorder should be assessed and patients should be offered or referred to psychosocial treatment based on their individual needs. A woman's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment, with appropriate medication management, during pregnancy. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
7. Counseling and testing for HIV should be provided (in accordance with state law). Tests for hepatitis B and C and liver enzymes are also suggested. Hepatitis A and B vaccinations is recommended for those whose hepatitis serology is negative.
8. MINOR REVISION Drug and alcohol testing should be used to monitor patients for adherence to medication and for use of illicit and controlled substances. This should be done with informed consent from the mother, realizing that there may be adverse legal and social consequences for substance use. State laws differ on reporting substance use during pregnancy. Laws that penalize women for substance use and for obtaining treatment serve to prevent women from obtaining prenatal care and worsen outcomes. For further clarity see The ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine guidance document.[14]
9. MINOR REVISION Care for pregnant women with opioid use disorder should be comanaged by a clinician experienced in obstetrical care and a clinician experienced in the treatment of opioid use disorder.
10. Hospitalization during initiation of methadone or buprenorphine may be advisable due to the potential for adverse events, especially in the third trimester.
11. MAJOR REVISION Methadone should be initiated at a dose range of 10–30 mg. Incremental doses of 5–10 mg is recommended every 3–6 hours, as needed, to treat withdrawal symptoms, to a maximum fist day dose of 30-40 mg.
12. MAJOR REVISION After initiation, clinicians should increase the methadone dose by no more than 10 mg approximately every 5 days. The goal is to maintain the lowest dose that controls withdrawal symptoms and minimizes the desire to use additional opioids.
13. MINOR REVISION 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 and/or split doses may be needed as pregnancy progresses. 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 OTP. After childbirth, doses may need to be adjusted (typically reduced) based on changes in weight and metabolism.
14. MAJOR REVISION If a woman becomes pregnant while she is receiving naltrexone, it may be appropriate to discontinue the medication if the patient and clinician agree that the risk of relapse is low. A decision to remain on naltrexone during pregnancy should be carefully considered by the patient and her clinician and should include a discussion on the insufficiency of research on risks (if any) of continued use of naltrexone. If the patient chooses to discontinue treatment with naltrexone and is at risk for relapse, treatment with methadone or buprenorphine should be considered.
15. MINOR REVISION Use of naloxone challenge (see glossary) to test for opioid dependence and risk of precipitated withdrawal is not recommended for pregnant women with opioid use disorder.
16. MINOR REVISION Unless otherwise contraindicated (see Part 8), mothers receiving methadone or buprenorphine for treatment of opioid use disorders should be encouraged to breastfeed.

Part 9: Special Populations: Individuals with Pain

1. MINOR REVISION For all patients with pain, it is important that the correct diagnosis is made and that pain is addressed. Alternative treatments including non-opioid medications with pain modulating properties, behavioral approaches, physical therapy, and procedural approaches (e.g., regional anesthesia) should be considered before prescribing opioid medications for pain.

2. MINOR REVISION If pharmacological treatment is considered, non-opioid analgesics, such as acetaminophen and NSAIDs, and non-opioid medications with pain modulating properties should be tried first.
3. MINOR REVISION For patients with pain who have an active opioid use disorder but are not in treatment, methadone or buprenorphine should be considered. The patient's opioid use disorder and pain should be stabilized and managed concurrently.
4. MAJOR REVISION For patients taking methadone or buprenorphine for the treatment of opioid use disorder, temporarily increasing the dose or dosing frequency (i.e. split dosing to maximize the analgesic properties of these medications) may be effective for managing pain. (Titration of methadone should follow the guidance in Part 4 of this guideline)
5. MAJOR REVISION For patients taking methadone for the treatment of opioid use disorder who have acute pain refractory to other treatments and require additional opioid-based analgesia, adding a short acting full agonist opioid to their regular dose of methadone can be considered to manage moderate to severe acute pain. The dose of additional full agonist opioid analgesic prescribed is anticipated to be higher than the typical dose necessary to achieve adequate analgesia in opioid-naïve individuals.
6. NEW Patients receiving buprenorphine for opioid use disorder who have moderate to severe acute pain refractory to other treatments and require additional opioid-based analgesia may benefit from the addition of as-needed doses of buprenorphine.
7. MAJOR REVISION The addition of a short-acting full agonist opioid to the patient's regular dose of buprenorphine can be effective for the management of severe acute pain in supervised settings, such as during hospitalization. The dose of additional full agonist opioid analgesic prescribed is anticipated to be higher than the typical dose necessary to achieve adequate analgesia in opioid-naïve individuals. Because of a lack of evidence, the committee was unable to come to consensus on whether this adjunct treatment can be safely prescribed in ambulatory care settings.
8. MAJOR REVISION Discontinuation of methadone or buprenorphine before surgery is not required. Higher-potency intravenous full agonists opioids can be used perioperatively for analgesia.
9. MINOR REVISION Decisions related to discontinuing or adjusting the dose of buprenorphine prior to a planned surgery should be made on an individual basis, through consultation between the surgical and anesthesia teams and the addiction treatment provider when possible.
10. MAJOR REVISION If it is decided that buprenorphine or methadone should be discontinued before a planned surgery, this may occur the day before or the day of surgery, based on surgical and anesthesia team recommendations. Higher-potency intravenous full agonists opioids can be used perioperatively for analgesia. Methadone or buprenorphine can be resumed post-operatively when the need for full opioid agonist analgesia has resolved, with additional considerations for post-operative pain management as described for acute pain above. The initial dose and titration should typically be determined by the prescriber. In general, pre-surgery daily doses of these medications can be resumed if they were withheld for less than 2-3 days.
11. MINOR REVISION Patients on naltrexone may not respond to opioid analgesics in the usual manner. Therefore, it is recommended that mild pain be treated with non-opioid analgesics, and moderate to severe pain be treated with higher potency NSAIDs (e.g. ketorolac) on a short-term basis.
12. MINOR REVISION Oral naltrexone should be discontinued 72 hours before surgery and extended-release injectable naltrexone should be discontinued 30 days before an anticipated surgery. (Reinitiation of naltrexone should follow the guidance in Part 6 of this guideline)
13. NEW Naltrexone's blockade of the mu opioid receptor can often be overcome when necessary with high potency full agonist opioids. In these instances, patients should be closely monitored in an emergency department or hospital setting.

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. MINOR REVISION Opioid agonists (methadone and buprenorphine) and antagonists (naltrexone) may be considered for treatment of opioid use disorder in adolescents. Federal laws and FDA approvals should be considered when recommending pharmacotherapy for adolescent patients.
3. MAJOR REVISION Psychosocial treatment is recommended in the treatment of adolescents with opioid use disorder. The risk benefit balance of pharmacological treatment without concurrent psychosocial treatment should be carefully considered and discussed with the patient and her or his parent or guardian as appropriate. A patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment of opioid use disorder, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
4. MINOR REVISION Concurrent practices to reduce infection (e.g., risk behavior reduction interventions) are recommended as components of comprehensive treatment for the prevention of blood-borne viruses (infections related to injection practices) and sexually transmitted infections.
5. Adolescents may benefit from treatment in specialized treatment programs that provide multidimensional services (See *The ASAM Criteria* guidelines).[2]

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

1. MINOR REVISION A comprehensive assessment including determination of mental health status and suicide risk should be used to 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. MINOR REVISION All patients with psychiatric disorders should be asked about suicidal ideation and behavior. Patients with a history of suicidal ideation or attempts should have adherence for opioid use disorder and psychiatric disorder medications monitored more closely.
4. MINOR REVISION Assessment for psychiatric disorder should occur at the onset of agonist or antagonist treatment. However, completion of all assessments should not delay or preclude initiating pharmacotherapy for opioid use disorder. If not completed before initiating treatment, assessments should be completed as soon as possible thereafter. Reassessment using a detailed mental status examination should occur after stabilization with methadone, buprenorphine, or naltrexone.
5. MAJOR REVISION Pharmacotherapy in conjunction with psychosocial treatment should be offered to patients with opioid use disorder and a co-occurring psychiatric disorder. A patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment of opioid use disorder, with appropriate mediation management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
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. NEW All FDA approved medications for the treatment of opioid use disorder should be available to individuals receiving healthcare within the criminal justice system. The treatment plan, including choice of medication, should be based on the patient's individual clinical needs.
2. MINOR REVISION Continuation of treatment after release results in a substantial reduction in all-cause and overdose mortality. Treatment should be individualized, and patients should receive complete information to make informed decisions in consultation with a medical and treatment team.
3. NEW Individuals entering the criminal justice system should not be subject to forced opioid withdrawal. Patients being treated for opioid use disorder at the time of entrance into the criminal justice system should continue their treatment. Patients with opioid use disorder who are not in treatment should be assessed and offered individualized pharmacotherapy and psychosocial treatment as appropriate.
4. MAJOR REVISION Initiation or maintenance of pharmacotherapy for the treatment of opioid use disorder is recommended for individuals within the criminal justice system (including both jails and prisons). Criminal justice staff should coordinate care and access to pharmacotherapy to avoid interruption in treatment. Patients should not be forced to transition from agonist (methadone or buprenorphine) to antagonist (naltrexone) treatment.
5. MAJOR REVISION Individuals in the criminal justice system who have opioid use disorder or who are experiencing opioid withdrawal should be offered a combination of pharmacotherapy and psychosocial treatment (based on an assessment of their individual psychosocial needs). A patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment of opioid use disorder, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
6. NEW If an OTP is not accessible, providers may need to transition individuals from methadone to buprenorphine. Effectively transitioning from methadone to buprenorphine can be challenging but can be achieved safely if managed by a provider experienced in the procedure.
7. MAJOR REVISION Risk for relapse and overdose is particularly high in the weeks immediately following release from prison and jails. Patients being treated for opioid use disorder while in prison or jail should be stabilized on pharmacotherapy (methadone, buprenorphine or naltrexone) and continue in treatment after their release. Patient care on reentry to the community should be individualized and coordinated with treatment providers in the community.
8. NEW Naloxone kits should be available within correctional facilities. Individuals with opioid use disorder should receive a naloxone kit prior to release, and individuals and families should be educated in how to administer naloxone.

Part 13: Naloxone for the Treatment of Opioid Overdose

1. MAJOR REVISION Naloxone should be administered in the event of a suspected opioid overdose.
2. MINOR REVISION Naloxone may be administered to pregnant women in cases of overdose to save the mother's life.
3. MINOR REVISION Patients who are being treated for opioid use disorder (as well as people with a history of opioid use disorder leaving incarceration) and their family members/significant others should be given naloxone kits or 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 carry and administer naloxone.

INTRODUCTION

Purpose

The American Society of Addiction Medicine (ASAM) developed the *National Practice Guideline for the Treatment of Opioid Use Disorder* (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*:

- Identifies current practices and outstanding questions regarding the safe and effective use of medications for the treatment of opioid use disorder.
- Uses a methodology that integrates evidence-based practices and expert clinical judgment to develop recommendations on best practices in opioid use disorder treatment.
- 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 brain disorder that can range in severity from mild to severe. Diagnosis of this disorder is based on a checklist of symptoms defined in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5) developed by the American Psychiatric Association.[1]

ASAM defines addiction as "a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences." Addiction is a serious biopsychosocial illness, meaning that biological, psychological, and social factors can all contribute to both the development of, and recovery from, this disease. *The ASAM Criteria* (discussed in Part 1) provide a framework for assessing how diverse biopsychosocial factors contribute to an individual patient's addiction and the type and intensity of treatment needed to support their recovery. ASAM views addiction as fundamentally a neurological disease involving 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. In this context, the preferred term by ASAM for this disorder is *addiction involving opioid use*.

A variety of substances commonly associated with addiction work on specific receptors and neurotransmitter systems in the nervous system. Pharmacological agents used in the treatment of addiction exert their effects via actions on specific receptors. Hence, the medications used in the treatment of addiction have efficacy based on their own molecular structure and the particular neurotransmitter receptors 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 U.S. Food and Drug Administration (FDA) for the treatment of opioid dependence (using DSM, 4th Edition [DSM-4] terminology), is also FDA-approved for the treatment of alcohol dependence (DSM-4).[6]

ASAM encourages clinicians, researchers, educators, and policy makers to use the term "addiction involving __" 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. However, 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

In 2018, an estimated 10.3 million people in the United States misused opioids (representing 3.7% of the population aged 12 or older), including 9.9 million pain reliever misusers and 808,000 heroin users. The 2018 National Survey of Drug Use and Health (NSDUH) found that 2.0 million persons in America met DSM 5 criteria for opioid use disorder.[8] 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.[17]

Mortality and Morbidity

Opioid misuse is associated with increased mortality. In the United States, more than 70,200 people died from drug overdoses in 2017; 47,600 of these deaths involved opioids.[18] These deaths include overdose from both illicit and prescription drugs. The sharpest increase occurred for deaths related to fentanyl and fentanyl analogs (other synthetic narcotics) which accounted for 28,400 overdose deaths in 2017. Drug overdose deaths involving heroin rose from 1,960 in 1999 to 15,482 in 2017, and drug overdose deaths from prescription opioids rose from 3,442 in 1999 to 17,029 in 2017.[18]

Risky behaviors associated with opioid misuse increase the risk of exposure to HIV, viral hepatitis, and other infectious agents through contact with infected blood or body fluids (e.g., semen) that results from sharing syringes and injection paraphernalia, or through unprotected sexual contact.[9] Nearly one in 10 new HIV diagnoses occur among people who inject drugs.[19] Importantly, injection drug use (IDU) is the highest-risk behavior for acquiring hepatitis C virus. More than 41,000 Americans were newly diagnosed with acute hepatitis C in 2016 with most new infections driven by IDU.[20]

Estimates of the total United States economic burden resulting from the opioid crisis vary widely. One estimate suggested an economic cost of $78.5 billion per year and included costs related to health care, lost productivity, addiction treatment, and criminal justice involvement.[21–23] Another estimate, from the Council of Economic Advisors, found an economic cost of $696 billion in 2018 alone including the value of lost lives, as well as increases in healthcare and substance abuse treatment costs, increases in criminal justice costs, and reductions in productivity.[23]

Scope of Guideline

This Practice Guideline was developed to assist clinicians in the evaluation and treatment of opioid use disorder. Although there are existing guidelines for the treatment of opioid use disorder, multiple new formulations of medications used for its treatment have been approved over the last few years. 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.

- Part 1: Contains guidelines on the evaluation of opioid use disorder
- Part 2: Provides recommendations regarding treatment options
- Part 3: Describes the management of opioid withdrawal
- Parts 4–6: Provide guidelines on medications for treating opioid use disorder
- Part 7: Describes psychosocial treatment used in conjunction with medications
- Parts 8–12: Provide guidelines for treating special populations and circumstances
- 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 (part 6)
4. Naloxone (part 13)
5. Clonidine (part 3)
6. Lofexidine (part 3)

Methadone, buprenorphine, naltrexone, and naloxone all act directly upon opioid receptors, particularly the mu-subtype. Methadone is a mu-receptor agonist; buprenorphine is a partial mu-receptor agonist; and naltrexone is an antagonist. Buprenorphine and naltrexone are also kappa opioid receptor antagonists which may contribute to their therapeutic effects.[24,25] 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.

Clonidine and lofexidine for the management of opioid withdrawal are described in Part 3: Treating Opioid Withdrawal of this Practice Guideline. Lofexidine has been used for the management of opioid withdrawal for many years and was approved for this indication by the FDA in May 2018. Clonidine is not FDA-approved for opioid withdrawal syndrome in the United States but has been in use, off label, in clinical settings for over 25 years.

ASAM recognizes that withdrawal management and withdrawal management medications could be potential topics for future comprehensive guideline development. ASAM will regularly review its published guidelines to determine when partial or full updates are needed (see 2019 Focused Update section below). The emergence of newly approved medications, medical devices and new research will be considered as part of this process. Since first publication of this guideline, ASAM developed a consensus document that addresses topics discussed in this Practice Guideline (The ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine).[26] For this, and any new ASAM guidelines published before a full 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. Clinicians, including physicians, nurse practitioners (NPs), physician assistants (PA), clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives involved in the assessment, diagnosis, and treatment of opioid use disorder. General practice clinicians (including those providing primary care, family practice, pediatric, obstetric, gynecologic, emergency, and urgent care services) are often first-line providers of medical care related to opioid use disorder and are also 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, coordinating 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. The document 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. ASAM recognizes that there are challenges to implementation of these guidelines in certain communities and settings, particularly in relation to the availability of all FDA approved medications for the treatment of opioid use disorder and access to psychosocial treatment in all settings. However, this guideline aims to set the standard for best clinical practice, providing recommendations for the appropriate care of patients with opioid use disorder in diverse settings. 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.[12] This process is particularly appropriate for these guidelines for two reasons. First, there are few randomized clinical trials (RCTs) 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 (e.g., nonrandomized studies, retrospective studies). The RCT is the gold standard for evidence-based medicine. When data are lacking from RCTs, 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 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 the criminal justice system. 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.

ASAM's Quality Improvement Council (QIC) was the oversight committee for 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 V-X.

The 2015 Guideline Committee was composed of 11 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.[7] Physicians with both allopathic and osteopathic training were represented on the Guideline Committee. The 2015 Guideline Committee was assisted by a technical team of researchers from the Treatment Research Institute (TRI) affiliated with the University of Pennsylvania and worked under the guidance of Dr. Kyle Kampman who led the TRI team as Principal Investigator in implementing the RAM. The 2019 focused update Guideline Committee under the guidance of the Committee Chair Dr. Kyle Kampman and Co-Chair Dr. Stephen Wyatt and assisted by RTI International (see section below titled 2019 Focused Update for methods specific to the focused update). 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.

2015 Guideline Development

Task 1: Review of Existing Guidelines

Review of Existing Clinical Guidelines. For the 2015 publication, all existing clinical guidelines that addressed the use of medications and psychosocial treatments in the treatment of opioid use disorders including special populations (e.g., 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, and/or naltrexone, as well as treatment of opioid overdose with naloxone.

Most 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 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, and how they have been addressed.

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. For the 2015 publication, 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. Articles were identified for inclusion in the review through searches conducted in two bibliographic databases (e.g., 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 January 2008 to December 2014. If 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 (i.e., 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.[26–28]

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 9-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 (e.g., increased life expectancy, relief of pain, reduction in anxiety, improved functional capacity) exceeds the expected negative consequences (e.g., 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 ratings were meant to identify consensus, or a lack thereof, 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 cannabis; 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. Not providing the service would be considered improper care.

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 (i.e., it is appropriate), and that they do so by such a margin that the provider must recommend the service. Of course, patients may decline to follow their provider's recommendations.[12]

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 QIC throughout February and March 2015.

Task 5: External Review

External Review. ASAM sought input from ASAM members, patient and caregiver groups, and other 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 2-week period of review and comment. The final draft Practice Guideline was submitted to the ASAM Board of Directors in April 2015.

2019 Focused Update New

Between September 2018 and July 2019, ASAM reconvened an independent committee (see page 2) to oversee a focused update of the Practice Guideline.[7] The purpose of the focused update was to develop new and revised recommendations based on a targeted review of new evidence and evolving clinical practice guidance. A full update of the guideline is scheduled to begin in 2021. ASAM's QIC worked with a technical team from RTI International (a not-for-profit research institution based in the Research Triangle Park in North Carolina) to develop and oversee the scope of work for the focused update.

The methods used to search the literature and subsequently develop guideline statements were consistent with the RAM methodology employed for the 2015 publication.[7,12] Criteria for inclusion in the focused update included new evidence and guidelines that were considered a) clinically meaningful and applicable to a broad range of clinicians treating addiction involving opioid use (including those related to comments received by ASAM from ASAM members), and b) urgently needed to ensure the guideline reflects

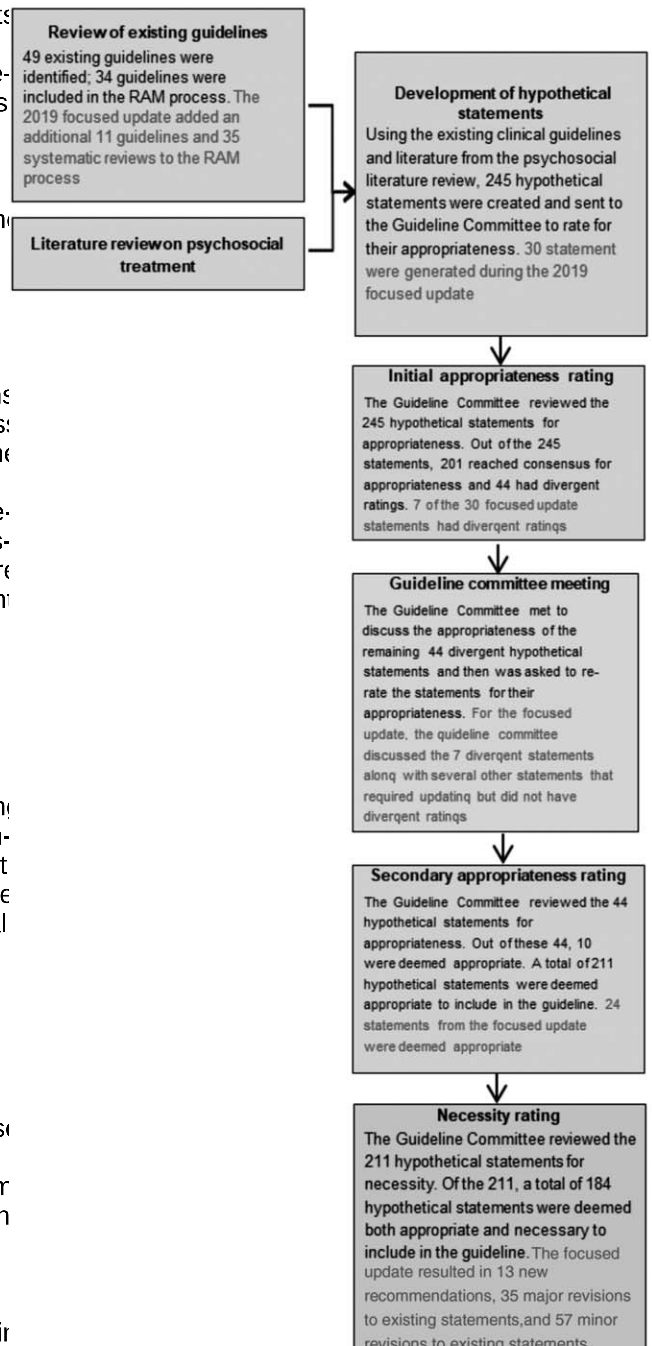

Exhibit 1. Methodology and Disposition of Results.

the current state of the science on the existing recommendations, aligns with other relevant practice guidelines, and reflects newly approved drugs and formulations. Relevant evidence and current practices not meeting these criteria will be reviewed and incorporated into the full update.

A search of Medline's PubMed database from January 1, 2014 to September 27, 2018 was conducted to identify new practice guidelines and relevant systematic reviews addressing the use of medications and psychosocial treatments in the treatment of opioid use disorders, including in special populations. The archives of the Clinical Guideline Clearinghouse, and key agency and society websites, including the Substance Abuse and Mental Health Services Administration (SAMHSA), the Agency for Healthcare Research and Quality, and the National Institute of Mental Health were also searched for additional guidelines. The FDA website was searched for recent relevant drug approvals and mandated label changes since publication of this *Practice Guideline* in 2015. A predefined set of inclusion and exclusion criteria (consistent with the 2015 process but meeting the above criteria for the focused update) were applied to identify practice guidelines and systematic reviews for inclusion in the *2019 Focused Update* Included guidelines and systematic reviews were not independently (i.e. outside of what was performed by the authors) assessed for risk of bias.

The literature search identified 210 unique practice guidelines and systematic reviews (208 were identified through initial searches on September 27, 2018; one additional systematic review was identified through a review of included guidelines; and a newly published systematic review from the Institute for Clinical and Economic Review (ICER) was added on October 26, 2018). Following dual review of titles and abstracts, 67 publications were retrieved for full-text review. Eleven practice guidelines and 35 systematic reviews met criteria for inclusion in the focused update. See Appendix I for a list of included practice guidelines and systematic reviews employed.

Key evidence from the identified practice guidelines; key findings from the systematic reviews; and newly approved FDA drugs, formulations and mandated label changes were abstracted and mapped to the existing ASAM recommendation statements to identify new and evolving clinical practice guidance, evidence, and recommendations. Using the RAM, hypothetical statements were developed and presented, along with supporting evidence, to the focused update Guideline Committee first for appropriateness rating and later, following revision, for necessity rating. Thirty statements were generated for the first round of appropriateness rating. Following round one, statements were revised, and 24 were presented for a second round of appropriateness and then necessity rating. The 24 newly generated statements for the focused update along with a review of the language in existing statements resulted in major revisions to 32 existing recommendations and the addition of 13 new recommendations. In addition, 55 statements underwent minor edits that did not change the substantive meaning of the original recommendation.

Exhibit 1 describes the methodology employed and presents the disposition of results for both the original and focused update guideline development process.

As with the 2015 guideline development process, supplementary literature searches were conducted to identify literature to help resolve differences among committee members during the statement rating process and to update key background information such as opioid use disorder statistics, recent changes to prescribing regulations, and FDA approvals. A handful of key systematic reviews and guidelines were released in the summer of 2019. These are referenced in places to support the updated guidelines but were not available during the RAM appropriateness and necessity rating process.

PART 1: ASSESSMENT AND DIAGNOSIS OF OPIOID USE DISORDER

Comprehensive Assessment

ASAM has published guidance on conducting assessments and diagnosing opioid use disorder in both *The ASAM Criteria* and the ASAM *Standards of Care for the Addiction Specialist Physician* (the ASAM Standards).[3,29] The ASAM Criteria provides comprehensive guidance on conducting a multidimensional assessment and determining the appropriate level of care for a given patient. Assessments are structured around six dimensions that provide a common language of holistic, biopsychosocial evaluation and treatment across substance use, physical health, mental health, and broad issues relevant to recovery. These dimensions include:

1. acute intoxication
2. biomedical conditions and complications
3. emotional, behavioral, or cognitive conditions or complications
4. readiness for change
5. continued use or continued problem potential
6. recovery/living environment

The ASAM Standards also 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.[29] The assessment does not necessarily need to occur in 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 more intensive level of care (see Part 11: Special Populations: Individuals with Co-occurring Psychiatric Disorders).

The assessments discussed in this section are critical for comprehensive treatment planning. However, since patients with opioid use disorder are at risk for significant harm – including overdose and overdose death – a delay in completion of each assessment should not delay or preclude the initiation of pharmacotherapy for opioid use disorder.

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 viral hepatitis, HIV, and TB; acute trauma; history of injection drug use and related infections (e.g. infective endocarditis, septic arthritis, osteomyelitis, abscesses, cellulitis, etc.); psychiatric, substance use, addictive behavior, and addiction treatment history; and any previous history of pharmacotherapy.

Physical Examination

As part of the comprehensive assessment of patients with opioid use disorder, a physical examination may be completed by the prescriber him/herself (the clinician authorizing the use of a medication for the treatment of opioid use disorder) or another member of the clinician's health system. The responsible clinician should assure that a current physical examination (in accordance with the ASAM Standards) is contained within the patient medical record before (or soon after) 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. Table 2 lists common signs of intoxication and withdrawal. In addition, the examination should evaluate objective signs of substance use disorders. See Table 3 for a list of physical signs of substance use disorders (including opioid use disorder).

The examination should also look for common physical signs of opioid use disorder (see Table 3), and physical health problems associated with substance use disorders including sleep disorders, infectious diseases (see Laboratory Tests section below), pain, cardiovascular disease, and liver disease. Special attention should be given to identifying injection drug use (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, the neck (i.e., external jugular), and the groin (i.e. femoral vein) may be used. Transition to injection in the neck, groin, and other sites may occur when the patient has exhausted more peripheral sites or when the patient is attempting to hide the signs of IDU. Classical physical signs are not always clear, it may take time (and subsequent visits) to establish whether a patient has an opioid use disorder.

TABLE 2. 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

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. Women of childbearing potential should be tested for pregnancy, and all women of childbearing potential should be queried regarding methods of contraception. Contraception and reproductive health are topics of discussion within the assessment process of female patients who are considering opioid use disorder treatment. Case management plans may need to include referral to gynecological services for female patients.[30] 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 laboratory testing should include a complete blood count, liver enzyme tests, and tests for TB, hepatitis B and C, and HIV. Testing for sexually transmitted infections should be strongly considered. Hepatitis A and B vaccination should be offered, if appropriate. A complete blood count and liver enzyme studies should be conducted to screen for liver dysfunction, infection, and other medical conditions. Abnormal results may require further investigation or referral.

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, including behavioral addictions (e.g. gambling disorder, gaming disorder, etc.). During the assessment process and physical examination, it is important for the clinician to assess for mental health status consistent with the ASAM Standards.

TABLE 3. Objective Physical Signs in Substance Use Disorders

System	Findings
Dermatologic	Abscesses, rashes, cellulitis, thrombosed veins, jaundice, spider angioma, palmer erythema, 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, gynecomastia
Gastrointestinal	Hepatomegaly, hernias

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."[29] A thorough medical and psychiatric history and family history is indicated as a component of this same standard. Patients who are identified 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 the severity of indicators for psychiatric instability. Indicators of psychiatric instability or disorder include acute suicidal or homicidal ideation, acute psychosis, and delirium.

Assessment for Substance Use and Treatment History

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

Completing a history of opioid misuse 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 use of controlled prescription medications, including opioids. They can serve as important resources for clinicians' use in completing full patient clinical assessments of opioid and other controlled substance use history, and it is recommended that they be utilized. As of June 2019, Missouri is the only U.S. state without a statewide PDMP. PDMPs vary with respect to how they are administered, who is granted access, and which medications are monitored.

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 Substance Use

Opioid use disorder often co-occurs with alcohol, nicotine, and other substance use disorders. Therefore, evaluation of co-occurring alcohol, nicotine, and substance use (including prescription medication misuse) 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. While the combined use of these drugs and opioids increases the risk of serious side effects, the harm caused by untreated opioid use disorder can outweigh these risks. Co-occurring substance use disorders should be addressed concomitantly. Patients with significant co-occurring substance use disorders, especially severe alcohol or sedative, hypnotic, or anxiolytic use, may require a higher level of care. When evaluating patients with opioid use disorder, the clinician should also consider assessing for misuse of other medications not traditionally considered (e.g. gabapentin). A 2017 systematic review reported that increasing numbers of patients are self-administering higher than recommended doses of gabapentinoids (gabapentin and pregabalin) to achieve euphoric highs. Among opioid users the reported prevalence of gabapentinoid misuse ranged from 3% to 68%.[31]

An evaluation of past and current substance use should be conducted to determine whether addiction involving other substances is present. For information on drug testing see The ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine guidance document.[14] 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 reevaluation of the level of care in which the patient is treated. However, if a more intensive level of care is not available or if a patient is unable or unwilling to engage in a more intensive level of care, that should not preclude or delay treatment initiation, including medications. In most cases, co-occurring substance use will not represent a medical emergency. In such cases, patients can begin treatment for both their opioid use disorder and co-occurring alcohol or substance use disorders.

Evidence suggest that individuals who are actively using other substances during opioid use disorder treatment may have a poorer prognosis.[32–34] The Guideline Committee cautioned against excluding patients from treatment for their opioid use disorder because they are using cannabis or other psychoactive substances. All co-occurring substance misuse should be addressed. While more research is needed, evidence demonstrates that patients in treatment have better outcomes than those not retained in treatment.[35–37] Suspension of opioid use disorder treatment may increase the risk for death from overdose, accidents, or other health problems. Continued use of cannabis or other psychoactive substances may impede treatment for opioid use disorder; thus, an approach that addresses all unprescribed substances is likely to result in the best outcomes. Further research is needed on the outcomes of patients in opioid use disorder treatment who are continuing the nonmedical use of other psychoactive substances.

Assessment for Nicotine Use

Nicotine 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.[37–39]

Assessment of Psychosocial and Environmental Factors

Clinicians should conduct an assessment of the patient's social history, readiness for change, and social and environmental factors (as outlined in The ASAM Criteria and the ASAM Standards) to identify facilitators and barriers to addiction treatment and long-term recovery, including pharmacotherapy.[2,29] In developing a comprehensive treatment plan for the patient with opioid use disorder, the patient should receive a multidimensional assessment (as described in The ASAM Criteria) The ASAM Criteria uses six dimensions to create a holistic biopsychosocial assessment of an individual to be used for service planning and treatment as described above.[2] The use of medications for patients with opioid use disorder can be appropriate across all levels of care. Pharmacotherapy is not a level of care in addiction treatment, but one component of multidisciplinary treatment. ASAM recommends that the use of medications in the treatment of addiction be part of a comprehensive treatment plan appropriate to the patient's needs and to the resources available in the patient's community. The use of medication(s) is 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 and laboratory testing, including drug testing. 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, prescriber confirmation of the diagnosis is required before medications are prescribed.

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 11 diagnostic criteria 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 12-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.[5]

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 several useful opioid withdrawal scales that can assist the clinician in evaluating patients with opioid use disorder by identifying and quantifying 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.[40] 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.[40] Finally, The Clinical Institute Narcotic Assessment (CINA) also includes 11 items and can help determine the severity of symptoms.[41]

Drug and Alcohol Testing

Urine drug testing, or other reliable biological tests for the presence of drugs and alcohol, can be used in the process of assessment and diagnosis to validate patient self-reported information and identify poly-substance use. Testing should also be used to monitor patients for adherence to medication and for use of illicit and controlled substances during treatment. A variety of toxicology tests are 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. Little research exists 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, and the treatment setting. Providers should also look to the test's detection capabilities and windows of detection to help determine the frequency of testing. Patients will likely require more testing early in treatment or during periods of relapse. Patients participating in treatment for opioid use disorder at OTPs are mandated by state regulations and the Federal law[42] to receive a minimum of eight drug tests per year, but may be tested more frequently based on clinical need. A 2017 consensus statement by ASAM states that the eight drug tests per year currently required should be viewed as a minimum. Many patients will require more frequent testing, and determinations about optimal frequency are best made on an individualized basis.[14] For more information on drug testing see The ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine guidance document.

In general, opioids, and most other substances of interest, are detectable in the urine for 1–3 days after use. A negative test does not rule out opioid use disorder or physical dependence. Urine, or other body fluid, testing is also helpful to identify use of other psychoactive substances.

Summary of Recommendations

Assessment Recommendations

1. The 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. NEW Comprehensive assessment of the patient is critical for treatment planning. However, completion of all assessments should not delay or preclude initiating pharmacotherapy for opioid use disorder. If not completed before initiating treatment, assessments should be completed soon thereafter.
3. MINOR REVISION Completion of the patient's medical history should include screening for concomitant medical conditions, including psychiatric disorders, infectious diseases (viral hepatitis, HIV, and tuberculosis [TB]), acute trauma, and pregnancy.
4. MINOR REVISION 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) should ensure that a current physical examination is contained within the patient medical record before (or soon after) a patient is started on pharmacotherapy.
5. MINOR REVISION Initial laboratory testing should include a complete blood count, liver enzyme tests, and tests for TB, hepatitis B and C, and HIV. Testing for sexually transmitted infections should be strongly considered. Hepatitis A and B vaccinations should be offered, if appropriate.
6. MINOR REVISION Women of childbearing potential should be tested for pregnancy, and all women of childbearing potential should be queried regarding methods of contraception.
7. MINOR REVISION Patients being evaluated for opioid use disorder, 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 (such as is outlined in *The ASAM Criteria* and *The ASAM Standards*).[2,29]
8. MINOR REVISION Opioid use disorder is often co-occurring with other substance use disorders. Evaluation of a patient with opioid use disorder should include a detailed history of other past and current substance use and substance use disorders.
9. MINOR REVISION The use of cannabis, stimulants, alcohol, and/or other addictive drugs should not be a reason to withhold or suspend opioid use disorder treatment. However, patients who are actively using substances during opioid use disorder treatment may require greater support including a more intensive level of care (see *The ASAM Criteria* and *The ASAM Standards*).[2,29]
10. MAJOR REVISION The use of benzodiazepines and other sedative-hypnotics should not be a reason to withhold or suspend treatment with methadone or buprenorphine. While the combined use of these medications increases the risk of serious side effects, the harm caused by untreated opioid use disorder can outweigh these risks. A risk-benefit analysis should be conducted, and greater support should be provided including careful medication management to reduce risks.[13]
11. MINOR REVISION A nicotine use query should be completed routinely for all patients and counseling on cessation of the use of tobacco products and electronic nicotine delivery devices (e.g. vaping) provided if indicated.
12. MINOR REVISION As part of comprehensive care the patient should receive a multidimensional assessment (as described in *The ASAM Criteria*), including an assessment of social and environmental factors to identify facilitators and barriers to addiction treatment and long-term recovery (including pharmacotherapy). Addiction is a complex biopsychosocial illness, for which the use of medication(s) is only one component of comprehensive treatment.[2]

Diagnosis Recommendations

1. MINOR REVISION Other clinicians may diagnose opioid use disorder, but confirmation of the diagnosis must be obtained by the prescriber 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. MINOR REVISION Validated clinical scales that measure withdrawal symptoms may be used to assist in the evaluation of patients with opioid use disorder.
4. MINOR REVISION Drug testing is recommended during the comprehensive assessment process, and during treatment to monitor patients for adherence to prescribed medications and use of alcohol, illicit, and controlled substances. The frequency of testing is determined by several factors including stability of the patient, type of treatment, and treatment setting. For additional information see The ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine guidance document.[14]

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 alcohol, cannabis, and/or other psychoactive substances.
3. Assessment and diagnosis of OUD is occurring increasingly in nontraditional settings, including hospital emergency departments and primary care. Implementation research is needed to determine the most effective tools and models for assessment and diagnosis in these settings.

PART 2: TREATMENT OPTIONS

Introduction

Once the diagnosis of opioid use disorder has been established, and the patient is determined to be medically and psychiatrically stable, the next task is to decide on a course of treatment. Treatment options include pharmacotherapy with one of three medications – methadone, buprenorphine, or naltrexone – and psychosocial treatment. Withdrawal management alone can be the first step but is not a treatment for opioid use disorder and should only be considered as a part of a comprehensive and longitudinal plan of care.

Behavior change is an important part of recovery, that may be facilitated by psychosocial treatment. However, these treatments take time to be effective. Medications work quickly to reduce the risk for overdose and overdose death. Thus, the combination of pharmacotherapy and psychosocial treatments, tailored to the individual's needs, is the recommended standard of care. Medications work rapidly to restore balance to the brain circuits impacted by addiction, reducing cravings and withdrawal symptoms and enabling patients to address the psychosocial factors that contribute to their disease and establish healthier patterns of behavior to support long-term recovery.

The choice among available treatment options should be a shared decision between the clinician and the patient. A number of factors should be considered in deciding what treatment(s) to choose. Among the first considerations are the priorities of the patient, for instance, is the patient open to pharmacotherapy? Does the patient have access to an OTP? What type of treatment setting does the patient prefer? Does the patient understand the pros and cons of the treatment medication options? 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 psychosocial treatment on its own; this is true for agonist, partial agonist, and antagonist medications. Evidence suggests that both methadone and buprenorphine maintenance treatments are superior to withdrawal management alone and both significantly reduce illicit opioid use.[15,36] Further, mortality is lower in patients on methadone or buprenorphine, as compared to those not undergoing treatment.[9,43] Methadone and buprenorphine also lower the risk of acquiring or spreading HIV infection.[44−46] In clinical studies, evidence favors buprenorphine, compared to no treatment, in decreasing heroin use and improving treatment retention.[35,47] Evidence also supports the efficacy of extended-release injectable naltrexone versus placebo for prevention of relapse to opioid use disorder.[48−50]

Pharmacotherapy Options

The medications covered in this *Practice Guideline* include those that have been approved by the FDA for the treatment of opioid use disorder. (See Appendix III for an overview of the main pharmacotherapy options and Appendix IV for a summary of available formulations). The FDA approvals for these medications have primarily been for 'opioid dependence' as defined in prior versions of the DSM, 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 (i.e. for individuals with new onset, mild opioid use disorder). In a study comparing opioid dependence from DSM-4 and opioid use disorder from DSM-5, optimal concordance occurred when four or more DSM-5 criteria were endorsed (i.e., the DSM-5 threshold for moderate opioid use disorder).[11]

The medications discussed in this *Practice Guideline* all have evidence supporting their safety and efficacy. While other medications have been used off-label to treat opioid use disorder the Guideline Committee has not issued recommendations on the use of these medications, with some exceptions (clearly noted in the text). 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 opioid withdrawal management (part 4).
2. Buprenorphine (partial mu-agonist) for opioid use disorder treatment and opioid withdrawal management (part 5).
3. Naltrexone (antagonist) for opioid use disorder relapse prevention (part 6).
4. Naloxone (antagonist) to reverse an opioid overdose (part 13).
5. Lofexidine (alpha-2 adrenergic agonist) for opioid withdrawal management (Part 3)
6. Clonidine (alpha-2 adrenergic agonist) for opioid withdrawal management (Part 3)

Since the 2015 publication of the *Practice Guideline*, in May 2018, the FDA approved the alpha-2 adrenergic agonist, lofexidine, as a treatment for withdrawal symptoms when opioids are abruptly discontinued.[51] Lofexidine will be covered in "Part 3: Treating Opioid Withdrawal". The only medication that is not FDA-approved for the treatment of opioid use disorder that will be covered in the *Practice Guideline* is another alpha-2 adrenergic agonist, clonidine, commonly used off-label 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, a 2016 Cochrane Collaboration meta-analysis found no difference between methadone and buprenorphine in retaining patients in treatment, reducing illicit opioid use or in reported adverse events.[52] A 2016 systematic review conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH) found methadone and buprenorphine/naloxone equally effective in reducing mortality, found that patients on buprenorphine/naloxone were more likely to abstain from opioid use, and found that more patients on methadone were retained in treatment.[53] The same review found that higher doses of both medications were more effective than lower doses.[50] An earlier Cochrane Collaboration meta-analysis also found methadone more effective than buprenorphine in retaining patients in treatment when buprenorphine doses are flexible but found that at fixed medium or high doses (16 mg and above), buprenorphine was as effective as methadone in retaining patients in treatment.[15,36] As noted earlier, there is strong evidence supporting the superiority of methadone and buprenorphine/(with or without naloxone) over medication-free treatment for reducing mortality, reducing opioid use, and promoting treatment retention.[15,54]

Opioid Dosing Considerations: Opioid Use Disorder Versus Chronic Pain

Guidelines for morphine milligram equivalents (MME) for opioid dosing for chronic pain are not applicable to the treatment of opioid use disorder. Higher MME dosage of medications used in the treatment of opioid use disorder are necessary and clinically indicated for effective treatment. The Centers for Disease Control and Prevention specifically advices against misapplication of the Guideline for Prescribing Opioids for Chronic Pain for patients receiving or starting medication for opioid use disorder.[55] See ASAM's public policy statement on *Morphine Equivalent Units/Morphine Milligram Equivalents* for additional details.[56]

Efficacy Considerations

Treatment Setting

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.[2]

In accordance with 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).[57] OTPs are subject to both Federal and state laws that have implications for patient treatment. Federal and state-licensed OTPs dispense and offer daily supervised dosing of methadone. Some OPTs also offer the option of daily supervised dosing of buprenorphine.

In accordance with Federal law 21 CFR §1306.07, physicians, NPs, PAs and other qualifying practitioners, in private practices, or various other types of private and public sector clinics, can be authorized to prescribe the partial opioid agonist buprenorphine. Buprenorphine, but not methadone, can be prescribed via regular outpatient prescriptions filled in a retail pharmacy (OBOT). This flexibility to provide OBOT is discussed more in Part 5: Buprenorphine. Existing regulations governing buprenorphine do not address the treatment facilities, but rather the individual clinician who prescribes buprenorphine (see Part 5: Buprenorphine for clinician qualifications associated with OBOT).

Methadone and buprenorphine can also be administered by non-waivered clinicians in emergency department and hospital settings under limited circumstances. Any clinician with the prescribing authority can provide either of these medications in a hospital inpatient setting:

for withdrawal management or maintenance pharmacotherapy for a patient as an adjunct to treatment for another medical condition (other than a substance use disorder);

to patients who have already been prescribed one of these medications and are admitted to the hospital, or treated in the emergency department;

In medical emergencies buprenorphine or methadone can be ordered and administered by non-waivered clinicians for no more than 3-days to treat acute withdrawal symptoms while arranging for the patient's referral for treatment as long as not more than one day's medication is administered or given to a patient at one time.[58]

Naltrexone can be prescribed in any setting by any clinician with the authority to prescribe medications. 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).

Clinicians should 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. Patients with active co-occurring alcohol, sedative, hypnotic, or anxiolytic use disorder (or who are in treatment for addiction involving the use of alcohol or other sedative drugs, including benzodiazepines or benzodiazepine receptor agonists) may need a more intensive level of care than can be provided in an office-based setting; this may also be true for persons who are regularly using alcohol or other sedatives, but do not meet the diagnostic criteria for a substance use disorder related to that class of drugs. However, OBOT services should not be withheld if the patient does not have access to or is unwilling to participate in a more intensive level of care. In these cases, the patient should be carefully monitored.

The use of benzodiazepines and other sedative-hypnotics should not be a reason to withhold or suspend treatment. According to the FDA, while the combined use of these drugs increases the risk of serious side effects, the harm caused by untreated opioid use disorder can outweigh these risks. A risk-benefit analysis should be conducted, and greater support should be provided including careful medication management to reduce risks. The prescribing of benzodiazepines or other sedative-hypnotics should be used with caution in patients with opioid use disorder, and particularly for patients who are prescribed methadone or buprenorphine.

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 associated with less physiological dependence. As discussed, methadone and buprenorphine (at sufficient doses) appear equally effective in reducing mortality, retaining patients in treatment and in reducing opioid use.[15,59] Evidence supports the efficacy of extended-release injectable naltrexone for relapse prevention compared to a placebo control.[48,49] A recent study comparing extended-release naltrexone to sublingual buprenorphine/naloxone found it was more difficult to initiate treatment with extended-release naltrexone resulting in a higher rate of early relapse among those randomized to extended-release naltrexone compared with those randomized to buprenorphine/naloxone.[60] Notably however, for those who successfully initiated treatment, extended-release naltrexone and buprenorphine/naloxone were similarly effective. Fatal overdose, non-fatal overdose, and other serious adverse events did not differ between treatment groups.[60] Similarly, a 12-week open-label RCT found extended-release naltrexone was similar to buprenorphine/naloxone in maintaining short-term abstinence from illicit opioids following successful initiation.[61]

Further study is needed on the relative effectiveness of extended-release naltrexone in reducing mortality compared with methadone or buprenorphine. A recent retrospective cohort study including data from more than 17,000 adults without cancer who survived an opioid overdose found decreased all-cause mortality and opioid-related mortality among patients treated with buprenorphine but could not draw any conclusions about the effect of naltrexone on mortality due to uncertainty in the estimates.[62]

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 (Table 4).

TABLE 4. Contraindications and Precautions for Pharmacotherapy Options[3,63,64]

Medication	Contraindications	Warnings and Precautions
Methadone	1. Hypersensitivity 2. Respiratory depression 3. Severe bronchial asthma or hypercapnia 4. Paralytic ileus	1. Head injury and increased intracranial pressure 2. Liver disease 3. Respiratory insufficiency 4. Cardiac conduction effects 5. Drug interactions with medications metabolized by cytochrome p450 enzymes principally CYP34A, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9and CYP2D6 6. Drugs co-administered with methadone, especially anti-retrovirals (including PrEP), anti-convulsants, and rifampin, should be evaluated for interaction potential 7. Diversion and misuse are possible 8. Physical dependence 9. Risk of life-threatening respiratory depression and death when used in association with benzodiazepines or other CNS depressants including alcohol, other opioid, and illicit drugs 10. Interaction with antidepressants and migraine medicines can cause a serious CNS reaction called serotonin syndrome 11. Addison's disease, a rare, but serious condition in which the adrenal glands do not produce adequate amounts of the hormone cortisol 12. Neonatal withdrawal after use of methadone during pregnancy
Buprenorphine (all formulations)	Hypersensitivity	1. Not recommended for patients with severe hepatic impairment 2. May cause sedation 3. Physical dependence 4. Risk of life-threatening respiratory depression and death when used in association with benzodiazepines or other CNS depressants including alcohol, other opioids, and illicit drugs 5. Precipitated withdrawal if used in patients physically dependent on full agonists opioids before the agonist effects have worn off 6. Interaction with antidepressants and migraine medicines can, in rare cases, cause a serious CNS reaction called serotonin syndrome 7. Addison's disease, a rare, but serious condition in which the adrenal glands do not produce adequate amounts of the hormone cortisol 8. Diversion and misuse are possible 9. Neonatal withdrawal after use of buprenorphine during pregnancy
Naltrexone (oral and injectable formulations)	1. Hypersensitivity reactions to naltrexone, or for injectable previous hypersensitivity reactions to polylactide-co-glycolide carboxymethylcellulose, or any other constituent of the diluent 2. Active hepatitis (hepatitis or if LFTs are > 3x normal) 3. Patients currently physically dependent on opioids, including partial agonists 4. Patients receiving opioid analgesics 5. Patients in acute opioid withdrawal	1. Vulnerability to overdose 2. Injection site reactions associated with injectable naltrexone 3. Precipitated opioid withdrawal 4. Administer IM injections with caution to patients with thrombocytopenia or a coagulation disorder 5. Risk of hepatotoxicity 6. Patient should be monitored for the development of depression and suicidality 7. Emergency reversal of opiate blockade may require special monitoring in a critical care setting 8. Eosinophil pneumonia has been reported in association with injectable naltrexone 9. Insufficient evidence of safety during pregnancy

Methadone

Methadone is frequently used to manage opioids withdrawal symptoms 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 (e.g., 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 anti-arrhythmic drugs, calcium channel blockers, some antipsychotics, and some antidepressants. (See Figure A for discussion of cardiac risk management)
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 mu opioid receptor agonist available in a variety of formulations, several which have been newly approved by the FDA since publication of the 2015 practice guideline (see Table 1). Buprenorphine is recommended 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 superior to lofexidine or clonidine in opioid withdrawal management.[47,57,65,66] Opioid withdrawal management (i.e. detoxification) on its own, without ongoing treatment for opioid use disorder, is not a treatment method for opioid use disorder and is not recommended. Ongoing maintenance medication, in combination with psychosocial treatment appropriate for the patient's needs, is the standard of care for treating opioid use disorder.

If the decision is made to taper, patients should be advised about the risk of relapse and other safety concerns, including increased risk of overdose and overdose death. Insufficient evidence is available on the relative effectiveness of different rates of tapering the buprenorphine dose. One trial did find that longer courses of buprenorphine with gradual tapering were superior to rapid tapering for withdrawal.[67]

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 office-based buprenorphine treatment.)

Buprenorphine should be used with caution for the following conditions:

1. Patients with current or 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.[68] Monitoring liver enzymes 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 (CNS) 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 (e.g., 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.[63,65,66,69]

In 2016, based on literature reviews involving the entire class of opioid pain medications and a review of reported adverse events, the FDA required the addition of warnings on all opioid product labels (including methadone and buprenorphine). Required warnings include the following:

1. There is a risk of life-threatening respiratory depression and death with concomitant use of methadone or buprenorphine with benzodiazepines or other CNS depressants.[70]
2. Opioids (including methadone and buprenorphine) can interact with antidepressants and migraine medicines to cause a serious CNS reaction called serotonin syndrome, in which high levels of the chemical serotonin build up in the brain and cause toxicity.[71]
3. Use of opioids (including methadone and buprenorphine) may lead to Addison's disease, a rare, but serious condition in which the adrenal glands do not produce adequate amounts of the hormone cortisol.[71]
4. Long-term use of opioids (including methadone and buprenorphine) may be associated with decreased sex hormone levels and symptoms such as decreased libido, impotence, or infertility.[70]

In September 2017, the FDA released an additional drug safety communication stating that based on additional review, the "FDA is advising that the opioid addiction medications buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other drugs that depress the CNS. The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks. Careful medication management by health care professionals can reduce these risks."[13]

While acknowledging the seriousness of each of these warnings, the Guideline Committee notes that when methadone and buprenorphine are used as prescribed and when treatment is carefully monitored by clinicians, these adverse events are rare and treatment benefits outweigh the risks of no treatment.

Naltrexone

Extended-release injectable naltrexone, administered every 3-4 weeks, is recommended for patients who are no longer physically dependent on opioids for preventing relapse in opioid use disorder (see Part 6: Naltrexone). Naltrexone is an opioid antagonist that blocks the effects of opioids and is used to prevent relapse in patients who are no longer dependent on opioids. 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 often lacks effectiveness due to poor medication adherence[72] and in a meta-analysis was not found to be superior to placebo or to no pharmacological treatments in treatment retention or illicit opioid use reduction.[73] Oral naltrexone should only be used under limited circumstances. For example, if taken daily, oral naltrexone can be effective in patients who are highly motivated or legally mandated to receive treatment, and/or when taking the medication is closely supervised. Clinicians may therefore want to reserve using oral naltrexone for patients who are able to comply with special techniques to enhance their adherence. While extended-release injectable naltrexone formulation may improve the adherence limitations of the oral formulation, studies suggest that adherence to extended-release naltrexone is lower than that of buprenorphine.[74]

Naltrexone is contraindicated in patients:

1. with hypersensitivity reactions to naltrexone.
2. 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. with current physical dependence on opioids, including partial agonists.
4. in acute opioid withdrawal.
5. who have failed the naloxone challenge test (see Glossary) or who test positive 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 who are pregnant or breastfeeding. Clinicians should discuss the paucity of research on the risks (if any) of naltrexone on fetal development.
3. Patients with liver impairment should complete liver enzyme tests before and during treatment with naltrexone to check for additional liver impairment.
4. 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.
5. Patients with co-occurring psychiatric disorders should be monitored for adverse events. Suicidal thoughts, attempted suicide, and depression have been reported.

Significant medication interactions to consider before starting naltrexone include the following:

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 (e.g. liver enzyme elevations).

Medication Management

Medication management should be provided in conjunction with pharmacotherapy. Medication management services focus on the appropriateness, effectiveness, and safety of medications for a given patient. These services include monitoring and evaluating the patient's response to medication (including ongoing misuse of substances) and medication adherence; dose titration as clinically indicated; education to ensure the patient understands their treatment plan, how to take their medications, and the importance of adherence; and provision of recommendations for other treatment and recovery support services as indicated. These services are intended to promote ongoing engagement in treatment, optimize the patient's medication response, and prevent relapse.

While some of the components of medication management, such as dose titration, should be performed by the prescriber, other components can be performed by other members of the patient's care team, either within the program or through referral. Medication management services as well as other services designed to improve treatment outcomes and prevent relapse should be coordinated across all providers involved in the patient's care.

PDMP Monitoring

Accessing PDMP data is advisable to check for other medications that the patient may be receiving. Due to 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. In addition, drug testing in combination with a patient's self-reported information about substance use is recommended as a monitoring tool during treatment. Note that medications dispensed through an OTP or other treatment program subject to the substance use disorder confidentiality regulations (42 CFR Part 2) and are typically not captured in state PDMPs.

Length of Treatment

While there is limited research on optimal length of addiction treatment, available research generally suggests that longer duration of treatment results in better outcomes. The National Institute on Drug Abuse's Principles of Drug Addiction Treatment notes that individuals progress through addiction treatment at various rates and positive outcomes are contingent on adequate treatment duration.[75] Generally, treatment participation for less than 90 days is of limited effectiveness, and treatment lasting significantly longer is associated with more positive long-term outcomes. For patients treated with methadone, 12 months is considered the minimum, and some patients will continue to benefit from this treatment for many years.[75]

Summary of Recommendations – Treatment Options

1. **MAJOR REVISION** All FDA approved medications for the treatment of opioid use disorder should be available to all patients. Clinicians should consider the patient's preferences, past treatment history, current state of illness, and treatment setting when deciding between the use of methadone, buprenorphine, and naltrexone.
2. **NEW** There is no recommended time limit for pharmacological treatment.
3. **MAJOR REVISION** Patients' psychosocial needs should be assessed, and patients should be offered or referred to psychosocial treatment based on their individual needs. However, a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacotherapy, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing individual needs.
4. **MINOR REVISION** The venue in which treatment is provided should be carefully considered. Methadone can only be provided in opioid treatment programs (OTPs) and acute care settings (under limited circumstances). Buprenorphine can be prescribed by waivered clinicians in any setting, including OTPs and office based opioid treatment (OBOT) in accordance with the Federal law (21 CFR §1301.28). Naltrexone can be prescribed in any setting by any clinician with the authority to prescribe medication. Clinicians should consider a patient's psychosocial situation, co-occurring disorders, and risk of diversion when determining which treatment setting is most appropriate (see *The ASAM Criteria* for additional guidance[1]).
5. **MINOR REVISION** Patients with active co-occurring alcohol use disorder or sedative, hypnotic, or anxiolytic use disorder (or who are in treatment for a substance use disorder involving use of alcohol or other sedative drugs, including benzodiazepines or benzodiazepine receptor agonists) may need a more intensive level of care than can be provided in an office-based setting. Persons who are regularly using alcohol or other sedatives, but do not meet the criteria for diagnosis of a specific substance use disorder related to that class of drugs, should be carefully monitored.
6. **MAJOR REVISION** The prescribing of benzodiazepines or other sedative-hypnotics should be used with caution in patients who are prescribed methadone or buprenorphine for the treatment of an opioid use disorder. While the combined use of these drugs increases the risk of serious side effects, the harm caused by untreated opioid use disorder can outweigh these risks. A risk-benefit analysis should be conducted when deciding whether to co-prescribe these medications.
7. 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.
8. **NEW** Opioid dosing guidelines developed for chronic pain, expressed in morphine milligram equivalents (MME), are not applicable to medications for the treatment of opioid use disorders.
9. **MINOR REVISION** Oral naltrexone for the treatment of opioid use disorder is often adversely affected by poor medication adherence and should not be used except under very limited circumstances. 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.
10. **MINOR REVISION** The Prescription Drug Monitoring Program (PDMP) should be checked regularly for the purpose of confirming medication adherence and to monitor for the prescribing of other controlled substances.

11. NEW Naloxone, for the reversal of opioid overdose, should be provided to patients being treated for, or with a history of, opioid use disorder. Patients and family members/significant others should be trained in the use of naloxone in overdose.

Areas for Further Research

1. Further research is needed to compare the advantages of agonists and antagonists in the treatment of opioid use disorder. Whereas methadone, buprenorphine, and extended-release injectable naltrexone are all superior to no treatment in opioid use disorder, less is known about their relative advantages.
2. Further research is needed to compare extended-release formulations in treatment of opioid use disorder (extended-release naltrexone vs extended-release buprenorphine).
3. Further research is needed on the comparative effectiveness of various health care settings and delivery systems (e.g., integrated delivery systems, health maintenance organizations, preferred provider organizations, point of service care etc.) for treatment of opioid use disorder.
4. Across a variety of sub-populations, further research is needed to better understand and characterize the effectiveness of and adherence to the different pharmacotherapy options to treat opioid use disorder.

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. Opioid withdrawal syndrome is rarely life-threatening, but deaths have been reported.[76] 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	8. Insomnia
2. Increased tearing	9. Sweating
3. Runny nose	10. Yawning
4. Dilated pupils	11. Abdominal cramping
5. Piloerection	12. Nausea
6. Agitation	13. Vomiting
7. Anxiety	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 a partial opioid 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 an intensive care unit.[77,78]

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[79]

The duration of 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 dependence is important to avoid precipitated withdrawal when introducing antagonists and partial agonists medications.

Withdrawal management can make withdrawal from opioids more comfortable. Given the high rate of relapse, opioid withdrawal management on its own, without ongoing pharmacotherapy, is not an effective treatment for opioid use disorder and is not recommended.[80] If withdrawal management alone, or withdrawal management followed by psychosocial treatment alone, is proposed the patient should be informed of the high risks of subsequent relapse, and the increased risk for overdose and overdose death, as compared to ongoing treatment with opioid agonists. Withdrawal management is not necessary or recommended for patients being referred for treatment with methadone or buprenorphine.

Assessment of Patients 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 (e.g., yawning, perspiration).[40]
Clinical Opioid Withdrawal Scale (COWS) is a clinical assessment for 11 medical signs and symptoms of opioid withdrawal (e.g., gastrointestinal distress).[81]
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 (e.g., I feel restless).[40]

The Clinical Institute Narcotic Assessment (CINA) scale is a mix of subjective and objective measures assessing 11 common signs and symptoms of opioid withdrawal.[41]

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 following inpatient versus outpatient withdrawal management.[82] For patients with significant or unstable physical or mental health issues, treatment in an inpatient setting with monitored withdrawal may be preferred.

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 involves the use of alpha-2 adrenergic agonists (FDA-approved lofexidine, and off-label use of clonidine) along with other non-narcotic medications to reduce withdrawal symptoms. Both strategies have advantages and disadvantages, and both are superior to placebo with respect to withdrawal severity and treatment completion. Methadone and buprenorphine are generally more effective in reducing the symptoms of opioid withdrawal, in retaining patients in withdrawal management, and in supporting the completion of withdrawal management.

With respect to withdrawal severity, recent evidence from systematic reviews suggests that methadone tapers or using alpha-2 adrenergic agonists for opioid withdrawal results in similar severity of withdrawal symptoms.[83] Buprenorphine tapers, on the other hand, may be more effective than alpha-2-adrenergic agonists in terms of withdrawal severity, duration, and treatment completion.[84] However, if treatment with naltrexone is planned, managing withdrawal with alpha-2-adrenergic agonists may enable a more rapid initiation. Buprenorphine and methadone appear to be similarly effective although data are limited.[84]

Withdrawal Management with Opioid Agonists

Methadone and buprenorphine are both recommended for management of opioid withdrawal and while comparative evidence remains limited, they appear to have comparable results in terms of reducing withdrawal severity and improving treatment retention and opioid abstinence. Withdrawal management with methadone must be done in an OTP or inpatient setting. As noted above, opioid withdrawal management on its own, without ongoing pharmacotherapy, is not a treatment method for opioid use disorder and is not recommended. Ongoing maintenance medication, in combination with psychosocial treatment appropriate for the patient's needs, is the standard of care for treating opioid use disorder. If the decision is made to taper, patients should be advised about the risk of relapse and other safety concerns, including increased risk of overdose and overdose death. 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 are specifically FDA-approved for withdrawal management, but they 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 agonist with a higher affinity for the mu-receptor than most full agonists such as heroin and oxycodone. Therefore, it is important that buprenorphine not be started until a patient is exhibiting objective signs of opioid withdrawal to avoid precipitated withdrawal. Opioid withdrawal usually occurs up to 12–18 hours after the last dose of a short-acting agonist such as heroin or oxycodone, and up to 24–48 hours after the last dose of a long-acting agonist such as methadone. Providers could consider sooner dosing of buprenorphine in an inpatient setting where the patient can be closely monitored.

With the increasing prevalence of fentanyl, concerns have been raised about whether the protocol for initiation onto buprenorphine should be modified for patients regularly using this or other high potency opioids. Fentanyl is short acting but has a long half-life (8-10 hours) and a relatively high affinity for the m-opioid receptor.[80] Some clinicians have recommended waiting until patients are in at least moderate withdrawal (COWS score of 13 or higher) before initiating buprenorphine. However, there is little existing evidence addressing this issue.

Withdrawal management with buprenorphine should start with an initial dose of 2-4 mg, titrated up as needed to suppress withdrawal (generally 4–16 mg per day). As noted above, opioid withdrawal management on its own, without ongoing pharmacotherapy, is not a treatment method for opioid use disorder and is not recommended. If the decision is made to taper, patients should be advised about the risk of relapse and other safety concerns, including increased risk of overdose and overdose death. Insufficient evidence is available on the relative effectiveness of different rates of tapering the buprenorphine dose. The duration of the tapering schedule can be as brief as 3–5 days or over 30 days. 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. One trial did find that longer courses of buprenorphine with gradual tapering were superior to rapid tapering for withdrawal.[65] Clinicians 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 have a long history of off-label use for the treatment of opioid withdrawal in the U.S. In May 2018, the FDA approved lofexidine for the mitigation of symptoms associated with abrupt withdrawal from opioids. Lofexidine is administered orally typically at a dose of three 0.18-mg tablets 4 times daily and can be continued for up to 14 days with dosing guided by symptoms. Lofexidine treatment should be discontinued with a gradual dose reduction over 2 to 4 days. 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. Alpha-2 adrenergic agonists are more effective than placebo in reducing severe withdrawal and in improving rates of treatment retention and completion. These medications can also be used concurrently with medications used to treat opioid use disorder. Alpha-2 adrenergic agonists can be used to treat withdrawal when patients taper off buprenorphine or methadone, and they can be used in preparation for initiation of extended-release naltrexone.[83]

Comparative data are limited but lofexidine and clonidine appear to be similarly effective in the treatment of opioid withdrawal with hypotension occurring less frequently with lofexidine.[83] Lofexidine should therefore be the preferred choice for withdrawal management in an outpatient setting where monitoring of blood pressure and management of hypotension is more difficult. Other agents in the same pharmacological family as clonidine, such as guanfacine (available in the U.S.) can also be used off-label as safe and effective agents in the management of opioid withdrawal.

Anesthesia-Assisted Withdrawal Management

Anesthesia-assisted opioid detoxification or 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.[85,86]

ASAM recommends against the use of UROD in the treatment of opioid withdrawal and stated these same recommendations in a policy statement. ASAM's position is in accordance with other guidelines. Serious complications including cardiac arrest and death have been reported with anesthesia-assisted withdrawal management.[87] The Centers for Disease Control and Prevention issued a warning in 2013 about severe adverse events including death from anesthesia-assisted withdrawal management.[88] 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.[89]

Summary of Recommendations – Treating Opioid Withdrawal

1. **MINOR REVISION** Using methadone or buprenorphine for opioid withdrawal management is recommended over abrupt cessation of opioids. Abrupt cessation of opioids may lead to strong cravings, and/or acute withdrawal syndrome which can put the patient at risk for relapse, overdose, and overdose death.
2. **MINOR REVISION** Opioid withdrawal management (i.e. detoxification) on its own, without ongoing treatment for opioid use disorder, is not a treatment method for opioid use disorder and is not recommended. Patients should be advised about the risk of relapse and other safety concerns, including increased risk of overdose and overdose death. Ongoing maintenance medication, in combination with psychosocial treatment appropriate for the patient's needs, is the standard of care for treating opioid use disorder.
3. **MINOR REVISION** 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. **MINOR REVISION** By regulation, opioid withdrawal management with methadone must be done in an OTP or an acute care setting (under limited circumstances). For patients withdrawing from short acting opioids the initial dose should typically be 20-30 mg per day and the patient may be tapered off in approximately 6-10 days.
5. **MAJOR REVISION** Opioid withdrawal management with buprenorphine should not be initiated until there are objective signs of opioid withdrawal. (See Part 3 for more information on the timing of initiating buprenorphine.) Once signs of withdrawal have been objectively confirmed, a dose of buprenorphine sufficient to suppress withdrawal symptoms is given (an initial dose of 2-4 mg titrated up as needed to suppress withdrawal symptoms).
6. **MAJOR REVISION** Alpha-2 adrenergic agonists (e.g., FDA-approved lofexidine and off-label clonidine) are safe and effective for management of opioid withdrawal. However, methadone and buprenorphine are more effective in reducing the symptoms of opioid withdrawal, in retaining patients in withdrawal management, and in supporting the completion of withdrawal management.
7. Opioid withdrawal management using ultra-rapid opioid detoxification (UROD) is not recommended due to high risk for adverse events or death. Naltrexone-facilitated opioid withdrawal management can be safe and effective but should be used only by clinicians experienced with this clinical method, and in cases in which anesthesia or conscious sedation are not employed.

Areas for Further Research

1. Further study is needed on methods to accelerate the withdrawal process and facilitate the introduction of antagonists. 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.[4] Although these techniques seem promising, more research is needed before these can be accepted as standard practice. Similarly, there are insufficient data to determine whether opioid antagonists (naltrexone, naloxone or both) in combination with alpha-2 adrenergic agonists (lofexidine and clonidine) reduce withdrawal duration or increase rates of retention in ongoing treatment with naltrexone.[84]
2. Further research is needed to make recommendations on the optimal duration of a buprenorphine taper, and to

compare the effectiveness of short versus long tapers with buprenorphine withdrawal management.

3. Further research is needed to evaluate the safety of inpatient as compared to outpatient withdrawal management.
4. Further research is needed to address whether the protocol for buprenorphine initiation should be modified for patients regularly using fentanyl and other high potency opioids.

PART 4: METHADONE

Background

Methadone, a slow-acting opioid agonist, 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 rewarding effect that can occur with other routes of administration while preventing withdrawal symptoms. Methadone has been used since the 1960 s to treat heroin addiction and remains an effective treatment option. Many studies have demonstrated its superiority to medication-free approaches.[36] In the United States, 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, and in acute care settings (under limited circumstances). 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, and for whom the therapeutic benefits of take-home doses outweigh the risks.

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 this treatment. Treatment with methadone has the following four goals:

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

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 conducted for patients with significant risk factors including any prior ECG demonstrating a QTc> 450 milliseconds, or a history suggestive of prior ventricular arrhythmia. ECG should also be considered when other risk factors for QT interval prolongation are present, including when high doses of methadone are being employed, patient or family history of cardiac risk factors, abnormal liver enzymes, electrolyte abnormalities, or the patient is taking medications known to prolong the QT interval. While there are no clear data on the threshold dose of methadone that confers risk for QT interval prolongation, the consensus of the committee is that ECG should be considered for patients receiving over 120 mg per day.[90] However, there is no research on the use of ECG data for improving patient outcomes. See Adverse Effect section below and "Part 2: Treatment Options: Contraindications and Precautions" for additional information.[91]

COURSE OF TREATMENT

Initiation

The previous version of these guidelines used the term induction instead of initiation. While the meaning is the same in this context, the guideline committee noted that this language did not align with the terminology used for other medical conditions and can make the process sound more difficult and complex than it is.

Initial dosing of methadone depends on the level of physical dependence. The recommended initial dose ranges from 10 to 30 mg, with reassessment as clinically indicated, typically in 2–4 hours when peak levels have been reached.[92] Reassessment in this time frame may not always be feasible, for example, when treatment initiation begins late in the day. In these cases, it may be more practical to reassess first thing in the morning. Timing of reassessment should not be a barrier to initiation of methadone.

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 the total dosage on the first day cannot exceed 40 mg.[42] For individuals with no or low opioid tolerance (e.g. patients transitioning from naltrexone, patients re-entering the community after residential treatment or incarceration [with no agonist treatment], patients re-initiating methadone after relapse), use a lower-than-usual dose (2.5 to 10 mg). Increase the dose slowly and with careful monitoring for all patients, with particular attention to patients who have not used opioids for 5 or more days, do not use opioids daily, or use less potent opioids (e.g., codeine).[93] Avoid using automated dosing increases to protect against the risk of overdose. Particular caution should be exhibited with patients with active cardiac disease or who have been prescribed other medications associated with QT interval prolongation.

Titration

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 to avoid increasing the dose before the full effect of the last dose has been realized. Doses do not correlate well with blood levels. Dosing should be based on the patient's response and can vary widely between patients. Methadone should generally not be increased every day but rather increased no more than 10 mg approximately every 5 days based on the patient's symptoms of opioid withdrawal or sedation. For example, 10 mg increases at intervals of 5 days or 5 mg increases at intervals of 2-3 days as symptoms persist. 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.[94–98] A relatively low dose of methadone (e.g., < 30 mg per day) can lessen acute withdrawal but is often not effective in suppressing craving. Patients should be educated to understand that the full benefits of methadone treatment take time and that it is common to feel unwell during the first few days of methadone titration.

Maintenance

Though a few patients respond to a maintenance dose of 30–60 mg per day, most patients fare better if their initial 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 found that patients have better outcomes, including retention in treatment, with higher doses (80–100 mg per day) than lower doses.[99,100] 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 availability of high potency opioids including fentanyl and other synthetic opioids.[92]

Adverse Effects

Higher methadone doses may be associated with increased risk of adverse effects, including prolongation of the QT interval and arrhythmias (torsades des pointes), which in some cases have been fatal (see Precautions section above).[101] The FDA issued a safety alert for methadone regarding these cardiac events.[102] 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.[103] Changing to buprenorphine or naltrexone maintenance should be considered when risks of QT prolongation are high as these medications do not seem to significantly prolong the QT interval. While there is limited evidence on effective screening strategies for preventing cardiac morbidity and mortality in patients treated with methadone, the Guideline Committee concurs with the recommendations from SAMHSA's TIP 63 which recommends that OTPs develop a cardiac risk management plan (Figure A).[91,104]

Figure A: Cardiac Risk Management Plan from SAMHSA's TIP 63[91]

''OTPs should consider the following elements in crafting a cardiac risk management plan:

1. An intake assessment of risk factors, which can include:
   a. Family history of sudden cardiac death, arrhythmia, myocardial infarction, heart failure, prolonged QTc interval, or unexplained syncope.
   b. Patient history of arrhythmia, myocardial infarction, heart failure, prolonged QTc interval, unexplained syncope, palpitations, or seizures.
   c. Current use of medications that may increase QTc interval (for a complete list, see www.crediblemeds.org/pdftemp/pdf / CompositeList.pdf; register for free for the most current list).
   d. Patient history of use of cocaine and methamphetamines (which can prolong the QTc interval).
   e. Electrolyte assessment (for hypokalemia or hypomagnesemia).
2. A risk stratification plan, which can include the following:
   a. Conduct an ECG for patients with significant risk factors at admission; repeat within 30 days. Repeat once a year and if the patient is treated with more than 120 mg of methadone per day.
   b. Discuss risks and benefits of methadone with patients with QTc intervals between 450 and 500 milliseconds. Adjust modifiable risk factors to reduce their risk.
   c. Do not start methadone treatment for patients with known QTc intervals above 500 milliseconds. If such an interval is discovered during treatment, have a risk/ benefit discussion. Strongly consider lowering the methadone dose, changing concurrent medications that prolong the QTc interval, eliminating other risk factors, and, if necessary, switching to buprenorphine. Include follow-up ECG monitoring.
   d. Consider providing routine universal ECG screening if feasible, although there is insufficient evidence to formally recommend doing so.''

Psychosocial Treatment

Because opioid addiction is a chronic relapsing disease, strategies specifically directed at relapse prevention are an important part of comprehensive treatment and can include counseling and/or other psychosocial treatments. Patients' psychosocial needs should be assessed, and patients should be offered or referred to psychosocial treatment based on their individual needs. However, there may be instances when pharmacotherapy alone results in positive outcomes. A patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment of opioid use disorder, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.

Family involvement in treatment can provide strong support for patient recovery; and family members may 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, close friends, clergy, employers, and case managers.

Monitoring Treatment

Federal and state-approved OTPs dispense and supervise administration of methadone. Treatment monitoring for methadone is subject to federal regulations (42 CFR Part 8). These regulations include requirements for medication administration, dispensing and use, as well as diversion control and drug testing.

Patients are seen daily at the beginning of their treatment for supervised dosing. Once patients are stabilized, take home doses of methadone may be dispensed based on criteria defined in the regulations. The stability of a patient is determined by the medical director based on several indicators which may include the absence of problematic alcohol and illicit drug use, participation in psychosocial treatment and other recovery-based activities, and productive occupational and social functioning. The regulations allow stable patients to be seen less frequently (once per week after six months in treatment and once every two weeks after a year in treatment).

Treatment should include relapse monitoring with frequent testing for alcohol and other relevant psychoactive substances. Testing for methadone metabolites (e.g., EDDP) is recommended to ensure adherence and detect possible diversion.

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. PDMP checks in combination with drug testing and a patient's self-reported information is recommended for monitoring substance use during treatment (See *The ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine* guidance document).[14]

Patients who discontinue agonist therapy should be made aware of the risks associated with an opioid overdose, and especially the increased risk of overdose death. Patients should also be made aware of other risks associated with intravenous drug use including the risk of infections (HIV, Hepatitis C, endocarditis, sepsis, etc.). Treatment alternatives including buprenorphine (see Part 5) and naltrexone (see Part 6), as well as opioid overdose prevention with naloxone (see part 13), should be discussed with any patient choosing to discontinue treatment.

Length of Treatment

There is no recommended time limit for treatment with methadone. Clinicians should not encourage patients to discontinue medication based on a pre-determined duration of treatment. While the optimal duration of treatment with methadone has not been established, it is known that relapse rates are high for most patients who drop out; thus, long-term treatment is often needed. While the research is limited, available research generally suggests that at longer duration of treatment result in better outcomes. The National Institute on Drug Abuse's Principles of Drug Addiction treatment notes that individuals progress through addiction Treatment at various rates and positive outcomes are contingent on adequate treatment duration.[74] Generally, treatment participation for less than 90 days is of limited effectiveness, and treatment lasting significantly longer is associated with more positive long-term outcomes. For patients treated with methadone, 12 months is considered the minimum, and some patients will continue to benefit from this treatment for many years.

Treatment duration depends on the response of the individual patient and is best determined by collaborative decision making 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.

TRANSITIONING BETWEEN TREATMENT MEDICATIONS

Transitioning from methadone to other opioid use disorder treatment medications may be appropriate in the following cases:

1. patient experiences intolerable methadone side effects;
2. patient has not been successful in attaining or maintaining their treatment goals through the initially chosen pharmacotherapy
3. patient wants to change and is a candidate for the alternative treatment.

Medication transitions 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.

Transitioning 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 transitioning causes significant discomfort. Patients should be closely monitored during such a transition 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 clinicians use careful initial dosing followed by rapid titration up to an appropriate maintenance dose. Patients should be experiencing mild to moderate opioid withdrawal before the transition. This would typically occur up to 24–48 hours after the last dose of methadone, after a sufficient time has elapsed for there to be minimal risk that the first dose of buprenorphine will precipitate significant withdrawal.

During office-based initiation of buprenorphine, the use of the COWS can be helpful in determining if patients are experiencing mild to moderate withdrawal.[80] A COWS score of 11–12 or more is generally indicative of sufficient withdrawal to allow a safe and comfortable initiation onto buprenorphine. For home-based initiation, clinicians should discuss with patients the importance of waiting for physical symptoms of opioid withdrawal (e.g. pupil dilation, goose bumps, gastrointestinal discomfort, etc.) before taking their first dose of buprenorphine to prevent precipitated withdrawal.

An initial dose of 2–4 mg of buprenorphine should be given. If withdrawal symptoms improve, the patient can be given additional 2–8 mg doses as needed to suppress withdrawal symptoms. 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.

Transitioning to Naltrexone

Patients transitioning from methadone to 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.[54] 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 – Methadone

1. MINOR REVISION Methadone is a recommended treatment for patients with opioid use disorder, who are able to give informed consent and have no specific contraindication for this treatment.
2. MAJOR REVISION The recommended initial dose of methadone ranges from 10 to 30 mg, with reassessment as clinically indicated (typically in 2 to 4 hours). Use a lower-than-usual initial dose (2.5 to 10 mg) in individuals with no or low opioid tolerance.
3. MAJOR REVISION Following initial withdrawal stabilization, the usual daily dose of methadone ranges from 60 to 120 mg. Some patients may respond to lower doses and some may need higher doses. Methadone titration should be individualized based on careful assessment of the patient's response and generally should not be increased every day. Typically, methadone can be increased by no more than 10 mg approximately every 5 days based on the patient's symptoms of opioid withdrawal or sedation.
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 prescribing non-monitored doses is appropriate.
5. MAJOR REVISION Patients' psychosocial needs should be assessed, and patients should be offered or referred to psychosocial treatment based on their individual needs, in conjunction with methadone in the treatment of opioid use disorder. However, a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay treatment with methadone, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
6. MINOR REVISION For patients who previously received methadone for the treatment of opioid use disorder, methadone should be reinstituted immediately if relapse occurs or if an assessment determines that the risk of relapse is high (unless contraindicated). Re-initiation of methadone should follow the recommendations above regarding initial dose and titration.
7. MINOR REVISION Strategies directed at relapse prevention are an important part of addiction treatment and should be included in any plan of care for a patient receiving opioid use disorder treatment or ongoing monitoring of the status of their disorder.
8. MINOR REVISION Transitioning from methadone to another medication for the treatment of opioid use disorder may be appropriate if the patient experiences dangerous or intolerable side effects or is not successful in attaining or maintaining treatment goals through the use of methadone.
9. MINOR REVISION Patients transitioning from methadone to buprenorphine in the treatment of opioid use disorder should ideally be on low doses of methadone before making the transition. 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 transitioning medications.
10. MINOR REVISION Patients transitioning from methadone to 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. MINOR REVISION There is no recommended time limit for pharmacological treatment with methadone. Patients who discontinue methadone treatment should be made aware of the risks associated with opioid overdose, and especially the increased risk of overdose death if they return to illicit opioid use. Treatment alternatives including buprenorphine (see Part 5) and naltrexone (see Part 6), as well as opioid overdose prevention with naloxone (see part 13), should be discussed with any patient choosing to discontinue treatment.

Areas for Further Research

1. Further research is needed to assess the effectiveness of specific types of psychosocial treatment in combination with methadone in OTP or inpatient settings. Treatment with methadone generally includes some psychosocial components, however, it is unclear when added psychosocial treatment improves patient outcomes, and which psychosocial treatments are beneficial to which patients.
2. Research is needed to evaluate the use of ECG in treatment with methadone in preventing adverse cardiac events.
3. Further research is needed on how to determine the optimal length of treatment with methadone for individual patients.
4. More research is needed on outcomes following transitions from methadone to other opioid use disorder treatment medications. For example, to what extent do different protocols for medication transitions affect short- and long-term treatment outcomes.

PART 5: BUPRENORPHINE

Background

Buprenorphine is recommended for the treatment of opioid use disorder. Buprenorphine relieves drug cravings without producing euphoria, and with reduced risk of dangerous and adverse effects compared with full agonist opioids. In addition to its pharmacological properties, an advantage of buprenorphine is that it can be prescribed in office-based treatment settings. The 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).[105] 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 access to 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 similar program and administration requirements to those for methadone.

Recent legislation has further expanded the types of practitioners who can prescribe buprenorphine for the treatment of opioid use disorder. The Comprehensive Addiction and Recovery Act (CARA) signed into law in July 2016 extended the authority to prescribe buprenorphine to qualifying NPs and PAs who obtain a waiver.[106] The SUPPORT for Patients and Community Act (Congress.gov) signed into law in October 2018 further expanded buprenorphine prescribing privileges (through October 1, 2023) to qualifying clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives.[107]

Formulations of Buprenorphine

For this *Practice Guideline*, recommendations using the term buprenorphine will refer generally to both the buprenorphine only (monoproduct) and the combination buprenorphine/naloxone (combination product) formulations. When recommendations differ by formulation it will be noted.

This *Practice Guideline* generally recommends using combination buprenorphine/naloxone for both withdrawal management and treatment of opioid use disorder, with special considerations for pregnant and breastfeeding women (See Part 8: Special Populations: Pregnant Women). Combination products contain naloxone (an opioid receptor antagonist), which is included to discourage intravenous use 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 generally averted when buprenorphine/naloxone is taken as prescribed, however a small amount of naloxone may be absorbed sublingually and can precipitate withdrawal. Patients dependent upon methadone or other long-acting opioid products may be more susceptible to this effect compared to those on short-acting opioid products. Buprenorphine/naloxone products have not been evaluated in adequate and well-controlled studies for initiation in patients who are physically dependent on long-acting opioid products. For this reason, buprenorphine monotherapy may be considered in patients taking long-acting opioids. Following initiation, the patient may then be transitioned to an extended-release or combination formulation.[68]

The FDA has approved numerous buprenorphine and buprenorphine/naloxone formulations (see Table 1). Newly approved formulations include extended-release injections, an extended-release subdermal implant, and generic versions of sublingual and buccal tablets and films. These new formulations provide a broad array of treatment options and their introduction onto the market provides patients and clinicians with much needed choice and flexibility when using buprenorphine for the treatment of opioid use disorder. Clinicians should use the new injectable products as indicated and be mindful of emerging evidence as it becomes available.

Bioequivalence information and charts for the various formulations of buccal and sublingual buprenorphine and buprenorphine/naloxone products 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 monoproduct sublingual tablets. Because of the possibility of slight differences in bioavailability between the different formulations of buprenorphine, patients transitioning from one form of buprenorphine to another should be monitored for efficacy and 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 this treatment. Treatment with buprenorphine has the following four goals:

1. suppress opioid withdrawal;
2. block the effects of illicit opioids;
3. reduce opioid craving and stop or reduce the use of illicit opioid;
4. 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.[108] Buprenorphine poses significantly lower risk for overdose compared to full agonist opioids due to the ceiling effects of buprenorphine for respiratory depression at higher 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. While the combined use of these drugs increases the risk of serious side effects, the harm caused by untreated opioid use disorder can outweigh these risks. However, patients with opioid use disorder and concurrent alcohol, sedative, hypnotic, or anxiolytic use disorders may need more intensive monitoring during office-based treatment with buprenorphine to minimize the risk of adverse events. Patients with these co-occurring disorders may be better treated in a setting with greater supervision such as an OTP. See "Part 2: Treatment Options: Contraindications and Precautions" for additional information.

Treatment Access

The DATA 2000, CARA 2016, and SUPPORT 2018, laws respectively allow qualifying physicians, NPs, PAs, and other qualifying practitioners including clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives to obtain waivers from SAMHSA to prescribe buprenorphine in their office practices or in a clinic setting.[105,107,109]

Both the monoproduct and combination product are approved by the FDA for the treatment of opioid use disorder and can be used in settings outside of an OTP. Providers who wish to prescribe buprenorphine for the treatment of opioid use disorder or withdrawal management must obtain a waiver under DATA 2000. Providers with DATA 2000 waivers may treat opioid use disorder with approved buprenorphine products in any practice settings in which they are otherwise credentialed to practice and in which such treatment would be medically appropriate (this may be subject to additional state regulations). The SUPPORT 2018 Act also made permanent the prescribing authority for PAs and NPs and allows waivered practitioners to immediately treat 100 patients at a time if the practitioner is board certified in addiction medicine or addiction psychiatry; or if the practitioner provides buprenorphine in a qualified practice setting.[107,110,111] The legislation also codified SAMHSA's regulations allowing certain practitioners to treat up to 275 patients. See Exhibit 4 "Clinician Qualifications for OBOT" for further details.

Exhibit 4: Clinician 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 U.S. Department of Health and Human Services, SAMHSA:

1. The physician holds a subspecialty board certification in addiction medicine or addiction psychiatry by The American Board of Preventive Medicine or the American Board of Psychiatry and Neurology
2. The physician holds a subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties.
3. The physician holds an addiction certification or board certification from ASAM or the American Board of Addiction Medicine. (ASAM certification was taken over by the American Board of Addiction Medicine in 2007.)
4. The physician holds a subspecialty board certification in addiction medicine from the American Osteopathic Association.
5. The physician has, with respect to the treatment and management of patients with opioid use disorder, completed not less than 8 hours of training (through classroom situations, seminars at professional society meetings, electronic communications, or otherwise) that is provided by 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.
6. 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.
7. 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) considered to demonstrate the ability of the physician to treat and manage patients with opioid use disorder.
8. The physician has such other training or experience as the Secretary considers to demonstrate the ability of the physician to treat and manage patients with opioid use disorder. 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.
9. The physician graduated in good standing from an accredited school of allopathic medicine or osteopathic medicine in the United States during the 5-year period immediately preceding the date on which the physician submits to the Secretary a written notification of the intent of the physician to begin dispensing drugs to patients for maintenance or detoxification treatment and successfully completed a comprehensive allopathic or osteopathic medicine curriculum or accredited medical residency that included not less than 8 hours of training on treating and managing patients with opioid use disorder and meets the statutory requirements.

Qualifying NPs and PAs, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives are required to:

1. be licensed under state law to prescribe schedule III, IV, or V medications for the treatment of pain;
2. obtain no fewer than 24 hours of initial training provided by one of the following organization: ASAM, American Academy of Addiction Psychiatry, American Medical Association, American Osteopathic Association, American Nurses Credentialing Center, American Psychiatric Association, American Association of Nurse Practitioners, American Academy of Physician Assistants, or any other organization that the Secretary of Health and Human Services determines is appropriate;
3. have such other training or experience as the Secretary determines will demonstrate the ability of the practitioner to treat and manage patients with opioid use disorder;
4. be supervised by, or works in collaboration with, a qualifying physician, if required by state law to prescribe medications for the treatment of opioid use disorder in collaboration with or under the supervision of a physician.

Initiation

The setting for initiation of buprenorphine should be carefully considered. During initiation, both office-based and home-based observation is considered safe and effective. Initiation within the clinician's office was traditionally recommended to reduce the risk of precipitated opioid withdrawal. However, home-based buprenorphine initiation has become increasingly common in recent years and is considered safe and effective under appropriate circumstances. Clinical judgement should be used to determine the most appropriate setting for a given patient and may include consideration of the patient's past experience with buprenorphine and assessment of their ability to manage initiation at home.[110,112,113]

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 initiation 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 who are currently dependent on opioids 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. Clinicians should use objective signs of opioid withdrawal before initiating buprenorphine initiation. Generally, buprenorphine initiation should occur at least 6–12 hours after the last use of heroin or other short-acting opioids, and 24–72 hours after the last use of long-acting opioids such as methadone.

During office-based initiation of buprenorphine, the use of the COWS can be helpful in determining if patients are experiencing mild to moderate withdrawal.[81] A COWS score of 11–12 or more is generally indicative of sufficient withdrawal to allow a safe and comfortable initiation onto buprenorphine. For home-based initiation, clinicians should discuss with patients the importance of waiting for physical symptoms of opioid withdrawal (e.g. pupil dilation, goose bumps, gastrointestinal discomfort, etc.) before taking their first dose of buprenorphine to prevent precipitated withdrawal.

With the increasing prevalence of fentanyl, concerns have been raised about whether the protocol for initiation onto buprenorphine should be modified for patients regularly using this or other high potency opioids. Fentanyl is short acting but has a long half-life (8–10 hours) and a relatively high affinity for the mu-opioid receptor.[80] Some clinicians have recommended waiting until patients are in at least moderate withdrawal (COWS score of 13 or higher) before initiating buprenorphine. However, there is little existing evidence addressing this issue.

Treatment decisions for patients transferring from another provider or with previous buprenorphine treatment experience should be individualized and based on the patient's medical and treatment history.

Dosing

At Initiation

The risk of precipitated withdrawal can be reduced by using a lower initial dose of buprenorphine. An initial dose of 2–4 mg and observation of the patient for signs of precipitated withdrawal is recommended. If 60–90 minutes have passed without the onset of withdrawal symptoms, then additional dosing can be done in increments of 2–8 mg. Repeat of the COWS during initiation can be useful in assessing the effect of buprenorphine dose. 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. One extended-release buprenorphine injections that received tentative FDA approval in December 2018 is indicated for initiation, stabilization and maintenance treatment when administered as a once-weekly or once-monthly injection. Only a single prior dose of transmucosal buprenorphine is required prior to initiation. Research on the use of the extended release formulations is emerging and, therefore, the clinical committee recommends that clinicians use these products as indicated and be mindful of further evidence as it becomes available.

After Initiation

Evidence suggests that buprenorphine doses of 16 mg or more per day or more may be more effective than lower doses at suppressing illicit opioid use.[15] The FDA generally recommends dosing to a limit of 24 mg per day, noting that 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 buprenorphine treatment.

Psychosocial Treatment

All patients should be assessed for psychosocial needs, and patients should be offered or referred to psychosocial treatment based on their individual needs. 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. However, a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment of opioid use disorder, with appropriate medication management. Motivational interviewing or enhancement should be used to encourage patients to engage in psychosocial treatment or recovery support services appropriate for addressing their individual needs. In the absence of added psychosocial treatment, clinicians may need to further individualize treatment plans to address the potential for issues related to adherence and diversion.

Monitoring Treatment

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

Accessing PDMP data is advisable to check for other medications that the patient may be receiving. Due to 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. In addition, drug testing in combination with a patient's self-reported information about substance use is recommended as a monitoring tool during treatment. Note that medications dispensed through an OTP or other treatment program subject to the substance use disorder confidentiality regulations (42 CFR Part 2) and are typically not captured in state PDMPs.

Urine drug testing is a reasonably practical and reliable method to test for adherence to medication and illicit drug use. However, other reliable biological tests for the presence of drugs may be used. The frequency of drug testing should be determined by a number of factors, including the stability of the patient, the type of treatment, and the treatment setting.[14] Drug testing is required a minimum of eight times per year for patients in OTP. Testing may include substances such as buprenorphine, illicit opioids, cocaine, methamphetamine, cannabis, and controlled prescription medications including benzodiazepines, opioids, and amphetamines. How often and exactly what drugs should be tested to optimize treatment has not been definitively established. See The ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine guidance document for more information.[14]

Continued substance use by the patient is not a sufficient reason to discontinue buprenorphine treatment. If a patient is continuing to use substances it may reflect the need for a change in treatment plan including a change in medication, dosage, or level of care.

Clinicians should take steps to reduce the chance of diversion. Diversion has been reported with both buprenorphine monotherapy and combination buprenorphine/naloxone.[114] Strategies to reduce the potential of diversion may include frequent office visits, 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 or accidental ingestion by young children. Unused medication should be disposed of safely.[73]

Patients who discontinue agonist therapy should be made aware of the risks associated with an opioid overdose, and especially the increased risk of overdose death. Patients should also be made aware of other risks associated with intravenous drug use including the risk of infections (HIV, Hepatitis C, endocarditis, sepsis, etc.). Treatment alternatives including methadone (see Part 4) and naltrexone (see Part 6), as well as opioid overdose prevention with naloxone (see part 13) should be discussed with any patient choosing to discontinue treatment.

Length of Treatment

There is no recommended time limit for treatment with buprenorphine. Clinicians should not encourage patients to discontinue medication based on a pre-determined duration of treatment. While the research is limited, available research generally suggests that longer duration of treatment results in better outcomes. The National Institute on Drug Abuse's Principles of Drug Addiction Treatment notes that individuals progress through addiction treatment at various rates and positive outcomes are contingent on adequate treatment duration.[75] Generally, treatment participation for less than 90 days is of limited effectiveness, and treatment lasting significantly longer is associated with more positive long-term outcomes.

Patients and clinicians should not take the decision to terminate treatment with buprenorphine lightly. Buprenorphine taper and discontinuation is a slow process and close monitoring is recommended. Buprenorphine tapering is generally accomplished over several months. Factors associated with successful termination of treatment with buprenorphine are not well described or supported by outcomes. Factors that may be taken into consideration or given emphasis in this decision include:

1. employment and financial stability;
2. housing stability;
3. engagement in mutual-help programs, or involvement in other meaningful activities;
4. sustained abstinence from opioid and other drugs during treatment;
5. positive changes in the psychosocial environment;
6. evidence of additional psychosocial supports;
7. persistent engagement in treatment for ongoing monitoring past the point of medication discontinuation.

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

Transitioning Between Treatment Medications

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

1. patient experiences intolerable side effects;
2. patient has not been successful in attaining or maintaining their treatment goals through the initially chosen pharmacotherapy;
3. patient wants to change and is a candidate for alternative treatment.

Transitioning to Methadone

Transitioning from buprenorphine to methadone does not typically result in any type of adverse reaction since moving from a partial opioid agonist to a full agonist does not pose a risk for precipitating withdrawal symptoms. No time delay is required in transitioning a patient from buprenorphine to treatment with methadone.

Transitioning to Naltrexone

Buprenorphine has a long half-life; 7–14 days should typically 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. A naloxone challenge (see Glossary) may be useful 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.[115] 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.

Summary of Recommendations – Buprenorphine

1. NEW Buprenorphine is a recommended treatment for patients with opioid use disorder, who are able to give informed consent and have no specific contraindication for this treatment.
2. MINOR REVISION For patients who are currently opioid dependent, buprenorphine should not be initiated until there are objective signs of opioid withdrawal to reduce the risk of precipitated withdrawal.
3. MAJOR REVISION Once objective signs of withdrawal are observed, initiation of buprenorphine should start with a dose of 2–4 mg. Dosages may be increased in increments of 2–8 mg.
4. MAJOR REVISION The setting for initiation of buprenorphine should be carefully considered. Both office-based and home-based initiation are considered safe and effective when starting buprenorphine treatment. Clinical judgement should be used to determine the most appropriate setting for a given patient and may include consideration of the patient's past experience with buprenorphine and assessment of their ability to manage initiation at home.
5. MAJOR REVISION Following initiation, buprenorphine dose should be titrated to alleviate symptoms. To be effective, buprenorphine dose should be sufficient to enable patients to discontinue illicit opioid use. Evidence suggests that 16 mg per day or more may be more effective than lower doses. There is limited evidence regarding the relative efficacy of doses higher than 24 mg per day, and the use of higher doses may increase the risk of diversion.[15]
6. NEW The FDA recently approved several new buprenorphine formulations for treatment of opioid use disorder (see Table 1). As data regarding the effectiveness of these products are currently limited, clinicians should use these products as indicated and be mindful of emerging evidence as it becomes available.
7. MAJOR REVISION Patients' psychosocial needs should be assessed, and patients should be offered or referred to psychosocial treatment based on their individual needs, in conjunction with buprenorphine in the treatment of opioid use disorder. However, a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay buprenorphine treatment, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
8. MINOR REVISION Clinicians should take steps to reduce the chance of buprenorphine diversion. Recommended strategies may include frequent office visits (e.g., weekly in early treatment); drug testing, including testing for buprenorphine and metabolites; and recall visits for medication counts. Refer to ASAM's Sample Diversion Control Policy for additional strategies to reduce the risk for diversion.[16]
9. MINOR REVISION Drug testing should be used to monitor patients for adherence to buprenorphine and use of illicit and controlled substances. For additional guidance see The ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine.[14]
10. MINOR REVISION Patients should be seen frequently at the beginning of treatment until they are determined to be stable.
11. When considering a transition from buprenorphine to naltrexone, providers should note that 7–14 days should typically 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.
12. MINOR REVISION When considering a transition from buprenorphine to methadone, there is no required time delay because the transition to a full mu-opioid agonist from a partial agonist does not typically result in an adverse reaction.
13. MINOR REVISION There is no recommended time limit for pharmacological treatment with buprenorphine. Patients who discontinue buprenorphine treatment should be made aware of the risks associated with opioid overdose, and especially the increased risk of death if they return to illicit opioid use. Treatment alternatives including methadone (see Part 4) and naltrexone (see Part 6), as well as opioid overdose prevention with naloxone (see part 13) should be discussed with any patient choosing to discontinue treatment.
14. MINOR REVISION 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.

Areas for Further Research

1. Further research is needed on the comparative effectiveness of newly approved buprenorphine formulations.
2. Further research is needed on how to determine the optimal length of treatment with buprenorphine for individual patients.
3. More research is needed to identify best practices for linking patients to continuing care when buprenorphine is initiated in an acute care setting.
4. Further research is needed to assess the effectiveness of specific types of psychosocial treatment in combination with buprenorphine. Evidence is needed to determine when added psychosocial treatment improves patient outcomes, and which psychosocial treatments are beneficial to which patients.

PART 6: NALTREXONE

Background

Extended release injectable 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 and extended-release injectable formulations.

Formulations of Naltrexone: Oral Versus Extended-Release Injectable

Except under special circumstances, evidence does not support the use of oral naltrexone as an effective treatment for prevention of opioid use disorder relapse. A meta-analysis of 1,158 participants in 13 randomized trials comparing treatment with oral naltrexone to either placebo or no medication found oral naltrexone was not superior to placebo or to no medication in either treatment retention or preventing return to illicit opioid use.[72] 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.[72,116]

Extended-release naltrexone is more effective than placebo[117] or no medication[118,119] in preventing return to illicit opioid use, and while not eliminating, reduces the poor adherence observed with the oral formulation. Extended-release injectable naltrexone should generally be administered every 4 weeks by deep IM injection in the gluteal muscle at a set dosage of 380 mg per injection. Some patients, including those who metabolize naltrexone more rapidly, may benefit from dosing as frequently as every 3 weeks. 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 common in patients with opioid use disorder.[120]

Patient Selection and Treatment Goals

Extended-release injectable naltrexone and under limited circumstances, oral naltrexone, are effective treatments recommended for patients to prevent relapse to opioid use disorder, are able to give informed consent, are fully withdrawn from opioids, and have no specific contraindications for this treatment.

Treatment with naltrexone generally has the following four goals:

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

Oral Naltrexone

In line with multiple other guidelines and government agencies, the Guideline Committee does not recommend the use of oral naltrexone except under very limited circumstances. Examples of limited circumstances under which treatment with oral naltrexone might be considered include: (1) for highly compliant and motivated patients such as safety-sensitive workers (e.g. police, firefighters, and healthcare professionals) or other individuals with high levels of monitoring and knowledge of negative consequences for nonadherence; (2) patients who wish to take an opioid receptor antagonist but are unable to take extended-release naltrexone (e.g. patients who may need an opioid analgesic within the next month); and (3) patients who may benefit from medication to prevent return to illicit drug use but cannot or will not take extended-release naltrexone and do not wish to be treated with (or do not have access to) opioid agonists. Under these limited circumstances in which oral naltrexone might be appropriate and following a negative naloxone challenge, the first oral dose of naltrexone can be 25 mg, increasing to 50 mg daily from day 2 of treatment. Those who tolerate a daily dose of 50 mg may be switched to a 3-day per week regimen (two 100-mg doses, followed by one 150-mg dose) for a total weekly dose of 350 mg. Adherence must be closely monitored when reducing to a 3-day per week regimen.

Extended-Release Injectable Naltrexone

As described in "Part 2: Treatment Options", extended-release injectable naltrexone is indicated for the prevention of relapse to opioid use disorder, following complete opioid withdrawal. It may be useful for patients who have contraindications to treatment with buprenorphine or methadone; patients for whom buprenorphine and methadone were not successful treatment modalities; individuals who are highly motivated to taper off their current agonist therapy; or patients who do not want to be treated with an agonist.

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 that do not reflect the degree to which they have lost tolerance, there is risk of an opioid overdose.[121] A similar dynamic occurs in patients who undergo withdrawal management with no meaningful follow-up treatment, or those who drop out of methadone or buprenorphine treatment.

Course of Treatment

Initiation

Before administering naltrexone, it is important that the patient has been adequately withdrawn 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

Extended-release injectable naltrexone can be given every 3–4 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 patients may metabolize naltrexone more rapidly. Patients may report experiencing break through cravings or being able to overcome the opioid receptor blockade at some point in the month. While there are no current studies evaluating more frequent dosing, the consensus of the Guideline Committee was that some patients, including those who metabolize naltrexone more rapidly, may benefit from dosing as frequently as every 3 weeks.

Under the limited circumstances for which oral naltrexone is appropriate, it 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.

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 injection site reactions specific to extended-release injectable naltrexone. To reduce injection site reactions in obese patients, a longer needle size may be used.[34]

Psychosocial Treatment

The psychosocial needs of patients treated with naltrexone should be assessed, and patients should be offered or referred to psychosocial treatment based on their individual needs. Research on extended-released injectable naltrexone as a standalone therapy without psychosocial treatment is limited. In addition, the types of psychosocial treatments studied have varied, and there is no clear guidance on what psychosocial treatment should be provided in conjunction with naltrexone. Therefore, as with buprenorphine and methadone, psychosocial treatment should be offered in conjunction with naltrexone treatment but a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay treatment of opioid use disorder with naltrexone, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment or support services appropriate for addressing their individual needs. In the absence of added psychosocial treatment, clinicians may need to further individualize treatment plans to address the potential for issues related to adherence.

However, given the paucity of evidence of demonstrated efficacy of extended release naltrexone without psychosocial treatment, methadone or buprenorphine may be the preferred pharmacotherapy in the absence of 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 until they are determined to be stable. The stability of a patient is determined by an individual clinician based on several indicators which may include abstinence from illicit drugs, participation in psychosocial treatment and other recovery-based activities, and 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 (note: medications dispensed through an OTP, and in some cases those prescribed or dispensed by treatment programs subject to the substance use disorder confidentiality regulations (42 CFR Part 2) are not captured in state PDMPs).

In addition, drug testing is recommended. Urine drug testing is a reasonably practical and reliable method to test for adherence to medication and illicit drug use. However, other reliable biological tests for the presence of drugs may be used. The frequency of drug testing will be determined by a number of factors, including the stability of the patient, the type of treatment, and the treatment setting.[14] Drug testing is required a minimum of eight times per year for patients in OTP. Testing may include substances such as illicit opioids, cocaine, methamphetamine, cannabis, and controlled prescription medications including benzodiazepines, opioids, and amphetamines. How often and exactly what drugs should be tested for to optimize treatment has not been definitively established. (For detailed recommendations see The ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine guidance document.)[14]

Length of Treatment

There is no recommended length of treatment with naltrexone. While the research is limited, available research generally suggests that longer duration of addiction treatment results in better outcomes. The National Institute on Drug Abuse's Principles of Drug Addiction treatment notes that individuals progress through addiction treatment at various rates and positive outcomes are contingent on adequate treatment duration.[75] Generally, treatment participation for less than 90 days is of limited effectiveness, and treatment lasting significantly longer is associated with more positive long-term outcomes. Duration of treatment should depend on the response of the individual patient, the patient's individual circumstances, and clinical judgment.

Patients who discontinue naltrexone treatment should be made aware of the increased risks associated with opioid overdose, and especially the increased risk of overdose death, if they return to illicit opioid use. Treatment alternatives including methadone (see Part 4) and buprenorphine (see Part 5), as well as overdose prevention with naloxone (see part 13) should be discussed with any patient choosing to discontinue treatment.

Transitioning Between Treatment Medications

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

1. patient experiences intolerable side effects;
2. patient has not been successful in attaining or maintaining their treatment goals through the initially chosen pharmacotherapy;
3. patient wants to change medications and is a candidate for alternative treatment.

Transfer of medications should be planned, considered, and monitored. Transitioning from an antagonist such as naltrexone to a full agonist (methadone) or a partial agonist (buprenorphine) is generally less complicated than transitioning from a full or partial agonist to an antagonist because there is no physical dependence associated with antagonist treatment. Patients being transitioned 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 low and titration to the maintenance dose should be done slowly and carefully. The clinician should discuss with the patient the potential for sedation, impairment, and fatigue, and carefully monitor these symptoms during initiation and titration. Patients should not be transitioned until a significant amount of the naltrexone is no longer in their system this varies but is typically about 1 day for oral naltrexone or 28 days for extended-release injectable naltrexone.

Summary of Recommendations – Naltrexone

1. MAJOR REVISION Extended-release injectable naltrexone is a recommended treatment for preventing relapse to opioid use disorder in patients who are no longer physically dependent on opioids, able to give informed consent, and have no contraindications for this treatment.
2. MAJOR REVISION Extended-release injectable naltrexone should generally be administered every 4 weeks by deep IM injection in the gluteal muscle at the set dosage of 380 mg per injection. Some patients, including those who metabolize naltrexone more rapidly, may benefit from dosing as frequently as every 3 weeks.
3. MAJOR REVISION Oral naltrexone is not recommended except under limited circumstances (see Part 6 for more details).
4. MAJOR REVISION Patients' psychosocial needs should be assessed, and patients should be offered or referred to psychosocial treatment based on their individual needs, in conjunction with extended-release naltrexone. A patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay naltrexone treatment, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
5. MINOR REVISION There is no recommended length of treatment with 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. MINOR REVISION Transitioning from naltrexone to methadone or buprenorphine should be planned, considered, and monitored. Transitioning from an antagonist such as naltrexone to a full agonist (methadone) or a partial agonist (buprenorphine) is generally less complicated than transitioning 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 transitioned from naltrexone to buprenorphine or methadone will not have physical dependence on opioids and thus the initial doses of methadone or buprenorphine should be low. Patients should not be transitioned until a significant amount of the naltrexone is no longer in their system, about 1 day for oral naltrexone or 28 days for extended-release injectable naltrexone.
7. MINOR REVISION Patients who discontinue naltrexone treatment should be made aware of the increased risks associated with opioid overdose, and especially the increased risk of overdose death, if they return to illicit opioid use. Treatment alternatives including methadone (see Part 4) and buprenorphine (see Part 5), as well as overdose prevention with naloxone (see part 13) should be discussed with any patient choosing to discontinue treatment.

Areas for Further Research

1. Further research is needed to test the relative effectiveness of extended-release injectable naltrexone as compared to agonist treatment, including methadone and extended-release injectable buprenorphine, in terms of treatment retention, substance use outcomes, and mortality.
2. Further research is needed on optimal withdrawal management and initiation protocols to initiate treatment with naltrexone and minimize the risk of precipitated withdrawal.
3. Further research is needed on outcomes related to administering extended-release injectable naltrexone every 3 weeks for individuals who metabolize naltrexone at higher rates.
4. Further research is needed on how to determine the optimal length of treatment with naltrexone for individual patients.
5. Further research is needed on the safety and efficacy of naltrexone for pregnant women.
6. Further research is needed to develop more effective strategies for improving adherence to extended-release injectable naltrexone.

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 most 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 should be individualized to each patient. Mutual help and other recovery support services complement professional treatment, but do not substitute for professional treatment.

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 and adherence to the treatment plan, including pharmacotherapy; 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 should be considered in conjunction with all pharmacological treatments for opioid use disorder. However, because of the potential harm associated with untreated opioid use disorder, a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment of opioid use disorder, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment or support services appropriate for addressing their individual needs. In the absence of added psychosocial treatment, clinicians may need to further individualize treatment plans to address the potential for issues related to adherence and diversion.

At a minimum, the psychosocial treatment component of the overall treatment program should include the following:

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

Psychosocial treatment may also include more intensive individual counseling and psychotherapy, contingency management, and mental health services. Broader psychosocial support includes recovery support services, case management, and more specific social needs assistance (e.g., employment, housing, legal services, etc.). Furthermore, interventions related to the provision of and education around harm reduction services including naloxone distribution, sterile syringe services, safe injection practices, risky behavior modification, contraception access (including the option of long-acting reversible contraception), etc., should be considered and incorporated into a patient's treatment plan as appropriate.

Efficacy of Psychosocial Treatments in Opioid Use Disorder

The systematic review of psychosocial interventions conducted as part of the 2015 guideline development process found that in general psychosocial therapy in combination with pharmacotherapy appears to improve clinical outcomes.[122] The review noted significant gaps in the literature including a lack of information about which psychosocial interventions are most effective in combination with specific medications. Of note, a systematic review examining the efficacy of adding specific, structured psychological treatments to standard agonist maintenance treatments with standard clinician-led medical management and counselling, did not improve treatment retention or decrease illicit opioid use during treatment compared to standard treatment with agonist medication.[27] This question has not been adequately studied for treatment with naltrexone.

Evidence is available demonstrating the superiority of some psychosocial treatments over others. Specifically, a 2008 meta-analysis compared 2,340 participants who received one of the following interventions: contingency management (CM), relapse prevention, cognitive behavioral therapy (CBT), or 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.[123]

While questions remain about which specific psychosocial therapies work best with which pharmacological treatments, there is widespread support for recommending psychosocial treatment as an important component of a patient's opioid use disorder treatment plan. The clinical committee recommends that patients routinely be assessed for psychosocial needs and offered or referred to psychosocial treatments appropriate to their individual needs as an adjunct to pharmacological treatments, with appropriate medication management. While a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment of opioid use disorder, motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment or support services appropriate for addressing their individual needs. In the absence of added psychosocial treatment, clinicians may need to further individualize treatment plans to address the potential for issues related to adherence, and diversion.

Peer Support and Mutual-Help Programs

Although not considered by ASAM to be a psychosocial treatment on their own, peer support services and mutual help programs are ancillary service that may be an effective adjunct to treatment. Peers who have successfully maintained recovery can provide mentoring, advocacy, and connections to community resources for individuals in treatment for opioid use disorder. Peer support services are increasingly offered in medical settings to help engage patients in treatment. Mutual-help programs may include 12-step programs such as Alcoholics Anonymous (AA), Narcotics Anonymous (NA), and Medication Assisted Recovery Anonymous (MARA). 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 accepting of 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.[29] 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 that psychosocial treatment is being offered and that the patient is progressing toward mutually agreed-upon goals. Treatment plans should be renegotiated when patients do not follow through with psychosocial treatment referrals and/or if it is determined that the treatment plan goals are not being advanced.

Psychosocial Treatment and Treatment with Methadone, Buprenorphine, or Naltrexone

As noted above, the current body of evidence suggests that in general psychosocial treatment in conjunction with pharmacotherapy improves patient outcomes. However, due to mixed findings, it is unclear which specific components of psychosocial treatment should be recommended. Some studies have found that the addition of psychosocial treatment improves adherence and retention in treatment[124–126] and improves withdrawal management outcomes,[27] while other studies found no benefit to specific psychosocial treatments[123] or report mixed findings.[27,127–129] The consensus of the committee, as noted above, is that all patients prescribed methadone, buprenorphine or naltrexone should be assessed for psychosocial needs and offered or referred to psychosocial treatments appropriate to their individual needs as an adjunct to pharmacological treatments. A patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay treatment of opioid use disorder with pharmacotherapy, with appropriate medication management. However, motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment or support services appropriate for addressing their individual needs.

Summary of Recommendations – Psychosocial Treatment in Conjunction With Medications for the Treatment of Opioid Use Disorder

1. MAJOR REVISION Patients' psychosocial needs should be assessed, and patients should be offered or referred to psychosocial treatment, based on their individual needs, in conjunction with any pharmacotherapy for the treatment of, or prevention of relapse to, opioid use disorder. However, a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment of opioid use disorder, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
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.

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. Further 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 can be effectively delivered in primary care settings.
5. Further research is needed on effective strategies for engaging patients in treatment, including models incorporating peer support.

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.[130] 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.

Opioid use is also associated with neonatal abstinence syndrome (NAS). NAS is the traditional term used to describe the constellation of withdrawal signs infants exhibit following prenatal exposure to substances that typically include opioid agonists. Federal agencies now commonly use the term neonatal opioid withdrawal syndrome (NOWS) to explicitly link in utero opioid exposure to subsequent infant withdrawal signs. Both terms are used in this document.

Pregnant women with active opioid use disorder should be treated with methadone or buprenorphine as the standard of care. Pregnant women with a history of opioid use disorder are also candidates for opioid agonist treatment if a return to opioid misuse is possible during pregnancy. Women who choose a medication-free approach using psychosocial modalities should be closely monitored.

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. However, completion of all assessments should not delay or preclude initiating pharmacotherapy for opioid use disorder. If not completed before initiating treatment, assessments should be completed soon thereafter. 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, and other healthcare providers that care for pregnant women 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. Pregnant women with opioid use disorder, as with non-pregnant individuals, also have a higher risk of HIV and viral hepatitis which can impact pregnancy, labor management and recommendations related to breastfeeding. On physical examination, some signs of injection drug use may include puncture marks, abscesses, or cellulitis.

Laboratory Tests

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 to pregnant women with opioid use disorder, according to state laws. Tests for hepatitis B and C and liver enzymes are also suggested. Hepatitis A and B vaccination is recommended for those whose viral hepatitis serology is negative.

All pregnant women should be screened for substance use with a validated screening tool. Women who screen positive for substance use should receive a comprehensive substance use assessment as part of obstetrical best practices.[14] 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 (See ASAM's Appropriate Use of Drug Testing in Clinical Addiction Medicineguidance document). State laws differ in terms of clinicians' reporting requirements of identified drug use (through either drug testing or self-report) 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. The American Congress College of Obstetricians and Gynecologists (ACOG) recommends that "in states that mandate reporting, policy makers, legislators, and physicians should work together to retract punitive legislation and identify and implement evidence-based strategies outside the legal system to address the needs of women with addictions."[133] Routine urine drug testing is not highly sensitive for many drugs and may result in false-positive and negative results that are misleading and potentially devastating for the patient. 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.[131]

For a pregnant patient with a history of addiction, providers should be aware that the postpartum period is a time of increased vulnerability. Therefore, assessment for relapse risk, which may include drug testing with patient consent, should be part of the postpartum visit.[14]

Imaging

Confirmation of a viable intrauterine pregnancy by sonography is sometimes required before acceptance into an OTP that is tailored specifically to pregnant women. Imaging is also useful for confirmation of gestational age and assessment of fetal weight if there is concern for fetal growth abnormalities.

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 adverse childhood experiences. Therefore, obtaining a psychosocial history is important when evaluating pregnant women for opioid use disorder.[132] The psychosocial needs of pregnant women being treated for opioid use disorder should be assessed and patients should be offered or referred to psychosocial treatment based on their individual needs. A woman's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment, with appropriate medication management, during pregnancy. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.

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 has minimal long-term developmental impacts on children relative to harms resulting from maternal use of heroin or misuse of prescription opioids. There is a risk of NOWS when opioid agonists are used during pregnancy; however, there is no evidence that methadone or buprenorphine taken for opioid use disorder in pregnancy results in higher rates of NOWS compared to illicit opioid use, and the risk of untreated opioid use disorder to the woman and fetus is much higher than the risk of NOWS. Therefore, women with opioid use disorder who are not in treatment should be encouraged to start opioid agonist treatment with methadone or buprenorphine 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 or post-partum, when they are at increased risk of relapse. Providers should also counsel pregnant women who use nicotine that reducing or stopping smoking can reduce the severity of NOWS.[133–138]

Treatment Management Team. Pregnancy in women with opioid use disorder should be managed by a clinician with experience in both obstetrical care and treatment of opioid use disorder or comanaged by a clinician with experience in obstetrical care and another clinician experienced in the treatment of opioid use disorder. 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, in combination with psychosocial treatment, rather than withdrawal management or psychosocial treatment alone 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. Providers should discuss treatment options as well as risks and benefits with the patient and document the decision in her chart. For women who are pregnant or breastfeeding, opioid agonist treatment with methadone or buprenorphine is the most appropriate treatment, taking into consideration effects on the fetus, neonatal abstinence syndrome, and impacts on perinatal care and parenting of young children.

There is a growing body of evidence comparing outcomes related to methadone and buprenorphine treatment during pregnancy.[133] Infants born to mothers treated with buprenorphine had shorter hospital stays (10 vs. 17.5 days), had shorter treatment durations for NOWS (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.[134] However, in this trial, mothers treated with buprenorphine were more likely to drop out of treatment compared to mothers treated with methadone. Larger studies are needed comparing the safety and effectiveness of buprenorphine versus methadone in the obstetric population.

Buprenorphine Monoproduct versus Buprenorphine/Naloxone. While the evidence on the safety and efficacy of naloxone in pregnant women remains limited,[135,136] the combination buprenorphine/naloxone product is frequently used and the consensus of the guideline committee is that the combination product is safe and effective for this population. Naloxone is minimally absorbed when these medications are taken as prescribed.

Naltrexone in Pregnancy. There is insufficient research on the safety and efficacy of naltrexone during pregnancy. If a woman becomes pregnant while she is receiving naltrexone, it may be appropriate to transition to methadone or buprenorphine, or to discontinue the medication if the patient and doctor agree that the risk of relapse is low. A decision to remain on naltrexone during pregnancy should be carefully considered by the patient and their clinician and should include a discussion on the paucity of information surrounding the risks (if any) of continued use of naltrexone. If the patient wishes to remain on naltrexone, it is important to obtain consent for ongoing treatment. If the patient decides to discontinue treatment with naltrexone and they are at risk of relapse, treatment with methadone or buprenorphine should be considered.

Naloxone in Pregnancy. The use of an antagonist such as naloxone to evaluate opioid dependence in pregnant women is contraindicated because induced withdrawal may precipitate preterm labor or fetal distress. Naloxone should be used in the case of maternal overdose to save the woman's life and can be used in the combination buprenorphine/naloxone product for opioid use disorder treatment as the naloxone is minimally absorbed when taken as prescribed.

Methadone Initiation

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.[134] NOWS can occur as a result of treatment with methadone but is easily treated. Patients should be counseled related to this risk. The NOWS risk to the fetus is significantly less than the risk of untreated opioid use disorder. 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 but there is no definitive evidence of abnormal development in children exposed to methadone in utero. Providers should also counsel pregnant women who use nicotine that reducing or stopping smoking can reduce the severity of NOWS.[133]

The optimum setting for initiation of treatment has not been evaluated in this population. Hospitalization during initiation of methadone may be advisable due to the potential for adverse events (e.g., overdose and adverse drug interactions), especially in the third trimester. The decision of whether to hospitalize a patient for initiation of methadone should consider the experience of the clinician as well as comorbidities and other risk factors for the individual patient. This is also an ideal time for the woman to be assessed by a social worker and case manager, and to initiate prenatal care if it has not been initiated earlier.

Methadone should be initiated at a dose range from 10 to 30 mg. Incremental doses of 5–10 mg can be given every 3–6 hours as needed to treat withdrawal symptoms, to a maximum first day dose of 30–40 mg. After initiation, clinicians should increase the methadone dose by no more than 10 mg approximately every 5 days (e.g., 10 mg increases at intervals of 5 days or 5 mg increases at intervals of 2–3 days as symptoms persist), if indicated, to maintain the lowest dose that controls withdrawal symptoms and minimizes the desire to use additional opioids. Considerations should be given to lowering the dose as clinically appropriate based on the patient's physiological response (e.g. sedation).

Buprenorphine Initiation. Initiation of buprenorphine may lead to withdrawal symptoms in patients with physical dependence on opioids. To minimize this risk, initiation should begin when a woman shows objective, observable signs of withdrawal, but before severe withdrawal symptoms are evidenced. This usually occurs at least 6–12 hours after the last dose of a short-acting opioid, and up to 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. The decision of whether to hospitalize a patient for initiation of methadone should consider the experience of the clinician as well as comorbidities and other risk factors for the individual patient.

With the increasing prevalence of fentanyl, concerns have been raised about whether the protocol for initiation onto buprenorphine should be modified for patients regularly using this or other high potency opioids. Fentanyl is short acting but has a long half-life (8–10 hours) and a relatively high affinity for the mu-opioid receptor. Some clinicians have recommended waiting until patients are in at least moderate withdrawal (COWS score of 13 or higher) before initiating buprenorphine. However, there is little existing evidence addressing this issue.

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.[139–142] The half-life of methadone falls from an average of 22–24 hours in nonpregnant women to 8.1 hours in pregnant women.[143] As a result, increased and/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 treatment response in this period. A common misconception is that that doses of methadone should decrease as pregnancy progresses; however, data refute this misconception. Refer to Part 4 for guidelines on appropriate methadone initiation and titration including the risk for overdose death. The risk and severity of NOWS are not correlated with methadone doses taken by the mother at the time of delivery and tapering of dose is not indicated.[144,145] After birth, the dose of methadone will likely need to be decreased (see Postpartum Treatment discussion below).

Buprenorphine Dosing. The need to adjust dosing of buprenorphine during pregnancy is less common compared with methadone. Clinicians may consider split dosing in patients who complain of discomfort and craving in the afternoon and evening. As with methadone, there is a risk of NOWS when buprenorphine is used during pregnancy; however, there is no evidence that buprenorphine taken for opioid use disorder in pregnancy results in higher rates of NOWS compared to illicit opioid use, and the risk of untreated opioid use disorder to the woman and fetus is much higher than the risk of NOWS. Buprenorphine treatment for pregnant women is associated with less severe NOWS compared to methadone. Buprenorphine dose should be determined based on the clinical response of the patient. The risk and severity of NOWS are not known to be correlated with buprenorphine doses taken by the mother at the time of delivery and tapering of dose is not indicated. In addition, for pregnant women who use nicotine, reducing or stopping smoking can reduce the severity of NOWS.[133,146]

Postpartum Treatment. Pharmacological treatment for opioid use disorder should be continued following delivery. If the dose of methadone was increased as pregnancy progressed to maintain therapeutic effects, the dosage will likely need to be reduced postpartum. Dosages should be titrated as needed to prevent sedation. It is less common for pregnant women to require dosage changes for buprenorphine. However, the patient should be monitored closely throughout pregnancy and the postpartum period and dosages adjusted as needed.[130]

The postpartum period can be a vulnerable time for women with opioid use disorder and research suggests that women are more likely to relapse during this time than during pregnancy. Women should routinely be screened for postpartum depression and providers should regularly evaluate the patient's needs for different or additional psychosocial treatments and support services.

Breastfeeding. Mothers receiving methadone or buprenorphine (including both the monoproduct and combination product) for the treatment of opioid use disorders should be encouraged to breastfeed in the absence of other contraindications. Guidelines from the Academy of Breastfeeding Medicine encourage breastfeeding for women treated with methadone who are enrolled in methadone programs.[147] Some of the benefits include improved maternal-infant bonding and favorable effects on NOWS.[148,149] It is not clear whether the favorable effects of breastfeeding on NOWS are related to the breast milk itself or the act of breastfeeding.[149,150] 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.[151]

Insufficient research exists on the risks (if any) of naltrexone for breastfeeding infants. There is limited data indicating that naltrexone is minimally excreted into breastmilk.[152] The decision to continue breastfeeding while taking naltrexone should be based on a mother's individual circumstances and preference. Clinicians should discuss this decision with the mother including a discussion on the risk of relapse, benefits of breastfeeding, and the risk to the infant of minimum exposure to naltrexone, noting that the data are unclear as to whether or not an actual risk exists. Consider monitoring the infant for exposure. If the infant is being treated for NOWS consider use of oral naltrexone instead of extended release naltrexone since the treatment can be more rapidly adjusted if there are signs of exposure.

Specialty advice should be sought for women with concomitant physical illnesses or other substance use disorders. Contraindications to breastfeeding include HIV-positive mothers. In addition, precautions and tailored advice are necessary for mothers who use alcohol, cocaine or amphetamine-type drugs.

Summary of Recommendations – Special Populations: Pregnant Women

1. NEW 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. MINOR REVISION Treatment with methadone or buprenorphine is recommended and should be initiated as early as possible during pregnancy.
3. MAJOR REVISION Pregnant women who are physically dependent on opioids should receive treatment using methadone or buprenorphine rather than withdrawal management or psychosocial treatment alone.
4. MAJOR REVISION A medical examination and psychosocial assessment are recommended when evaluating pregnant women for opioid use disorder. However, completion of all assessments should not delay or preclude initiating pharmacotherapy for opioid use disorder. If not completed before initiating treatment, assessments should be completed as soon as possible thereafter.
5. Obstetricians and gynecologists, and other healthcare providers that care for pregnant women, 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.
6. MAJOR REVISION The psychosocial needs of pregnant women being treated for opioid use disorder should be assessed and patients should be offered or referred to psychosocial treatment based on their individual needs. A woman's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment, with appropriate medication management, during pregnancy. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
7. Counseling and testing for HIV should be provided (in accordance with state law). Tests for hepatitis B and C and liver enzymes are also suggested. Hepatitis A and B vaccinations is recommended for those whose hepatitis serology is negative.
8. MINOR REVISION Drug and alcohol testing should be used to monitor patients for adherence to medication and for use of illicit and controlled substances. This should be done with informed consent from the mother, realizing that there may be adverse legal and social consequences for substance use. State laws differ on reporting substance use during pregnancy. Laws that penalize women for substance use and for obtaining treatment serve to prevent women from obtaining prenatal care and worsen outcomes. For further clarity see The ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine guidance document.[14]
9. MINOR REVISION Care for pregnant women with opioid use disorder should be comanaged by a clinician experienced in obstetrical care and a clinician experienced in the treatment of opioid use disorder.
10. Hospitalization during initiation of methadone or buprenorphine may be advisable due to the potential for adverse events, especially in the third trimester.
11. MAJOR REVISION Methadone should be initiated at a dose range of 10–30 mg. Incremental doses of 5–10 mg is recommended every 3–6 hours, as needed, to treat withdrawal symptoms, to a maximum fist day dose of 30–40 mg.
12. MAJOR REVISION After initiation, clinicians should increase the methadone dose by no more than 10 mg approximately every 5 days. The goal is to maintain the lowest dose that controls withdrawal symptoms and minimizes the desire to use additional opioids.
13. MINOR REVISION 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 and/or split doses may be needed as pregnancy progresses. 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 OTP. After childbirth, doses may need to be adjusted (typically reduced) based on changes in weight and metabolism.

14. **MAJOR REVISION** If a woman becomes pregnant while she is receiving naltrexone, it may be appropriate to discontinue the medication if the patient and clinician agree that the risk of relapse is low. A decision to remain on naltrexone during pregnancy should be carefully considered by the patient and her clinician and should include a discussion on the insufficiency of research on risks (if any) of continued use of naltrexone. If the patient chooses to discontinue treatment with naltrexone and is at risk for relapse, treatment with methadone or buprenorphine should be considered.
15. **MINOR REVISION** Use of naloxone challenge (see glossary) to test for opioid dependence and risk of precipitated withdrawal is not recommended for pregnant women with opioid use disorder.
16. **MINOR REVISION** Unless otherwise contraindicated (see Part 8), mothers receiving methadone or buprenorphine for treatment of opioid use disorders should be encouraged to breastfeed.

Areas for Further Research

1. Further research is needed on the safety of combination buprenorphine/naloxone and new extended-release formulations for use in pregnancy.
2. Further research is needed to investigate the safety of naltrexone while pregnant or breastfeeding.
3. Further research is needed to determine what, if any, clinical benefit there is to routinely drug testing pregnant women.
4. Further research is needed on the comparative effectiveness of inpatient versus outpatient settings for methadone and buprenorphine initiation for pregnant women.
5. Further research is needed on best treatment approaches for pregnant or breastfeeding women who cannot or will not take medication for opioid use disorder.

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 and it is critical to manage pain safely and effectively. There are three general scenarios (listed below), in which patients with opioid use disorder could require pain care:

1. patients with an untreated and active opioid use disorder;
2. patients under opioid use disorder treatment with opioid agonists;
3. 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 pain treatment be identified. Nonpharmacological treatments (e.g., psychosocial treatments, physical therapy) have been shown to be effective for many types of pain and should be considered.

If pharmacological treatment is considered, then non-opioid analgesics such as acetaminophen and NSAIDs and other medications with pain-modulating properties, such as gabapentinoids, tricyclic antidepressants, norepinephrine-serotonin reuptake inhibitors, and dissociative anesthetics (e.g., ketamine) may be useful and should be considered first. Additional non-opioid interventions such as regional anesthesia should also be considered.

The presence or history of substance use disorder alone, including opioid use disorder, should not preclude the use of opioids to treat pain. Pain treatment should be coordinated with the opioid use disorder treating clinician to help optimize pain care (e.g., by using split rather than single daily doses of buprenorphine or methadone to maximize the analgesic properties of these medications as discussed below) and reduce the potential for relapse.

Pain Management in Patients with Opioid Use Disorder

Methadone or buprenorphine may be considered for patients with pain who have an active opioid use disorder but are not undergoing treatment. Both methadone and buprenorphine have analgesic effects. Transition to opioid agonist treatments can help comanage pain and opioid use disorder.

Methadone and Pain Management

Patients prescribed methadone for opioid use disorder should receive pain management in the same way as other patients, ideally through consultation with a clinician experienced in pain care and their addiction treatment provider.

Acute and Chronic Pain Management

Temporarily increasing the methadone dose or dosing frequency may be effective for managing pain. Splitting the daily methadone dose across 3–4 doses per day can maximize the analgesic properties of this medication. The withdrawal and craving suppressing properties of methadone typically last for 24–36 hours while its analgesic effects typically last for 6–8 hours. As discussed in Part 4 of this guideline, methadone has a long half-life and care should be taken to avoid too rapid dose increases (refer to Part 4 for guidance on titration).

If the patient has pain refractory to this and non-opioid treatment strategies and requires additional opioid-based analgesia, the addition of a short acting full-agonist opioid can be considered to manage moderate to severe acute pain.[153] The dose of additional full agonist opioid analgesic prescribed is anticipated to be higher than the typical dose necessary to achieve adequate analgesia in opioid-naïve individuals.[154,155] Patients on methadone maintenance who have co-occurring chronic pain should optimally be treated by a clinician experienced in the treatment of pain in consultation with their opioid treatment program.

Buprenorphine and Pain Management

Acute Pain Management

As a partial mu-opioid agonist, buprenorphine has analgesic properties. Temporarily increasing buprenorphine dosing and/or dividing the dose may be effective for acute pain management. As discussed above, this split dosing strategy better aligns the dosing with buprenorphine's analgesic properties. The analgesic effects of buprenorphine last for approximately 6–8 hours while the withdrawal and craving suppressing properties last for approximately 24 hours. When moving to split dosing the clinician should ensure that the patient has not missed their last non-split dose. Increasing the daily dose of buprenorphine by 20–25% and splitting it into 3–4 doses can often adequately address acute pain.

Patients receiving buprenorphine for opioid use disorder who have acute pain refractory to other treatments and require additional opioid-based analgesia may also benefit from the addition of as-needed doses of buprenorphine. Adding a short-acting full agonist opioid to the patient's regular dose of buprenorphine can also be effective for managing severe acute pain. The guideline committee recommends that this may be considered in supervised settings, such as during hospitalization. The dose of additional full agonist opioid analgesic prescribed is anticipated to be higher than the typical dose necessary to achieve adequate analgesia in opioid-naïve individuals. Because of a lack of evidence, the committee was unable to come to consensus on whether this adjunct treatment can be safely prescribed in ambulatory care settings. An increased risk of relapse and overdose are the main concerns when prescribing a full opioid receptor agonist for acute pain care in individuals with opioid use disorder.

In situations when a full opioid agonist is needed for pain management, discontinuation of buprenorphine is not required. However, if the decision is made to discontinue buprenorphine during the treatment of severe pain to allow for more mu opioid receptor availability, patients should be monitored closely because high doses of a full agonist may be required. As the partial agonist effect dissipates, the full agonist effect may lead to over-sedation and respiratory depression.

Chronic Pain Management

Split dosing of buprenorphine (with dosing every 6–8 hours) may be adequate for chronic pain management in many patients with opioid use disorder and chronic pain. Chronic opioid therapy, especially at high doses, may heighten pain sensitivity.[155] Some evidence suggests that patients experiencing substantial pain on high doses of full agonist opioids experience improved pain management when transitioned to buprenorphine.[156] Overall, buprenorphine therapy carries a lower risk of adverse effects, especially overdose, compared to full agonist opioids.

Naltrexone and Pain Management

Patients on naltrexone may not respond to opioid analgesics in the usual manner. Mild pain may be treated with non-opioid analgesics such as acetaminophen and NSAIDs. High potency NSAIDs, such as Ketorolac, may be prescribed for moderate to severe pain. The use of NSAIDs should be time-limited due to risk of adverse effects, including gastritis.

Emergency pain management options in patients taking naltrexone, which may optimally be used in combination when appropriate, include the following:

1. regional anesthesia;
2. conscious sedation with benzodiazepines or ketamine;
3. nonopioid options in general anesthesia;
4. over-riding the naltrexone blockade with high-potency opioids.

Naltrexone's blockade of the mu-opioid receptor can also often be overcome, when necessary, with high potency full agonist opioids.[64] Higher doses are typically needed to override the opioid receptor blockade so this should be done in an inpatient setting with monitoring of vitals. Use of high potency opioids, with high affinity for the mu-opioid receptor, administered intravenously is recommended in these cases.

Considerations for Surgery

Patients Treated with Methadone or Buprenorphine

Discontinuation of methadone or buprenorphine before surgery is not required. Higher-potency intravenous full agonists opioids can be used perioperatively for analgesia in addition to the patient's regular dose of methadone or buprenorphine (except to the extent that doses may be skipped during the NPO [nothing per orem] period before surgery).[156–158] Discontinuation of methadone or buprenorphine is also not recommended before elective cesarean section.

Since buprenorphine has a high affinity for the mu-opioid receptor there were initially concerns that full-opioid agonists would not be effective for treating pain in patients taking this medication. However, research has demonstrated that the addition of full-opioid agonists can be effective for the treatment of pain in these patients.[157,158] Reducing the dose of buprenorphine to provide more mu-opioid receptor availability and increase the efficacy of full opioid agonists co-administered with buprenorphine has been suggested, but there is insufficient research on this topic. Decisions related to discontinuing or adjusting the dose of buprenorphine prior to a planned surgery should be made on an individual basis, through consultation between the surgical and anesthesia teams and the addiction treatment provider when possible.

If it is decided that buprenorphine or methadone should be discontinued before a planned surgery, this may occur the day before or the day of surgery, based on surgical and anesthesia team recommendations. Higher-potency intravenous full agonists opioids can be used perioperatively for analgesia. Methadone or buprenorphine can be resumed post-operatively when the need for intravenous analgesia has resolved, with additional considerations for post-operative pain management as described for acute pain above. The pre-surgery daily doses of these medications can be resumed if they are withheld for a short period of time (up to 2–3 days). If these medications are withheld for a longer period of time they may need to be reinitiated gradually by the prescribing clinician after the need for full opioid agonist analgesia has resolved. For guidance on re-initiation and titration see Parts 4 and 5 of this guideline.

Patients Treated with Naltrexone

Oral naltrexone should be discontinued at least 72 hours before elective surgery if pain management with opioids is anticipated. Extended-release naltrexone should be stopped at least 30 days before surgery, and oral naltrexone may be used temporarily (until 72 hours prior to the planned surgery). 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). Re-initiation of naltrexone should be coordinated with the opioid use disorder treating clinician. See the naltrexone section for recommendations related to initiation.

Summary of Recommendations – Special Populations: Individuals With Pain

1. (MINOR REVISION) For all patients with pain, it is important that the correct diagnosis is made and that pain is addressed. Alternative treatments including non-opioid medications with pain modulating properties, behavioral approaches, physical therapy, and procedural approaches (e.g., regional anesthesia) should be considered before prescribing opioid medications for pain.
2. (MINOR REVISION) If pharmacological treatment is considered, non-opioid analgesics, such as acetaminophen and NSAIDs, and non-opioid medications with pain modulating properties should be tried first.
3. (MINOR REVISION) For patients with pain who have an active opioid use disorder but are not in treatment, methadone or buprenorphine should be considered. The patient's opioid use disorder and pain should be stabilized and managed concurrently.
4. (MAJOR REVISION) For patients taking methadone or buprenorphine for the treatment of opioid use disorder, temporarily increasing the dose or dosing frequency (i.e. split dosing to maximize the analgesic properties of these medications) may be effective for managing pain. (Titration of methadone should follow the guidance in Part 4 of this guideline)
5. (MAJOR REVISION) For patients taking methadone for the treatment of opioid use disorder who have acute pain refractory to other treatments and require additional opioid-based analgesia, adding a short acting full agonist opioid to their regular dose of methadone can be considered to manage moderate to severe acute pain. The dose of additional full agonist opioid analgesic prescribed is anticipated to be higher than the typical dose necessary to achieve adequate analgesia in opioid-naïve individuals.
6. (NEW) Patients receiving buprenorphine for opioid use disorder who have moderate to severe acute pain refractory to other treatments and require additional opioid-based analgesia may benefit from the addition of as-needed doses of buprenorphine.
7. (MAJOR REVISION) The addition of a short-acting full agonist opioid to the patient's regular dose of buprenorphine can be effective for the management of severe acute pain in supervised settings, such as during hospitalization. The dose of additional full agonist opioid analgesic prescribed is anticipated to be higher than the typical dose necessary to achieve adequate analgesia in opioid-naïve individuals. Because of a lack of evidence, the committee was unable to come to consensus on whether this adjunct treatment can be safely prescribed in ambulatory care settings.
8. (MAJOR REVISION) Discontinuation of methadone or buprenorphine before surgery is not required. Higher-potency intravenous full agonists opioids can be used perioperatively for analgesia.
9. (MINOR REVISION) Decisions related to discontinuing or adjusting the dose of buprenorphine prior to a planned surgery should be made on an individual basis, through consultation between the surgical and anesthesia teams and the addiction treatment provider when possible.
10. (MAJOR REVISION) If it is decided that buprenorphine or methadone should be discontinued before a planned surgery, this may occur the day before or the day of surgery, based on surgical and anesthesia team recommendations. Higher-potency intravenous full agonists opioids can be used perioperatively for analgesia. Methadone or buprenorphine can be resumed post-operatively when the need for full opioid agonist analgesia has resolved, with additional considerations for post-operative pain management as described for acute pain above. The initial dose and titration should typically be determined by the prescriber. In general, pre-surgery daily doses of these medications can be resumed if they were withheld for less than 2–3 days.
11. (MINOR REVISION) Patients on naltrexone may not respond to opioid analgesics in the usual manner. Therefore, it is recommended that mild pain be treated with non-opioid analgesics, and moderate to severe pain be treated with higher potency NSAIDs (e.g. ketorolac) on a short-term basis.
12. (MINOR REVISION) Oral naltrexone should be discontinued 72 hours before surgery and extended-release injectable naltrexone should be discontinued 30 days before an anticipated surgery. (Reinitiation of naltrexone should follow the guidance in Part 6 of this guideline)
13. (NEW) Naltrexone's blockade of the mu opioid receptor can often be overcome when necessary with high potency full agonist opioids. In these instances, patients should be closely monitored in an emergency department or hospital setting.

Areas For Further Research

1. Research on optimal acute and chronic pain management strategies for patients on medications for opioid use disorder.
2. Studies on the safety and effectiveness of adding full agonist opioid analgesics to the patient's baseline buprenorphine dose in non-acute care settings are needed.
3. Further research is needed on chronic pain management for patients with opioid use disorder.