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American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use

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The Centers for Disease Control have recently described opioid use and resultant deaths as an epidemic. At this point in time, treating this disease well with medication requires skill and time that are not generally available to primary care doctors in most practice models. Suboptimal treatment has likely contributed to expansion of the epidemic and concerns for unethical practices. At the same time, access to competent treatment is profoundly restricted because few physicians are willing and able to provide it. This ''Practice Guideline'' was developed to assist in the evaluation and treatment of opioid use disorder, and in the hope that, using this tool, more physicians will be able to provide effective treatment. Although there are existing guidelines for the treatment of opioid use disorder, none have included all of the medications used at present for its treatment. 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. This Practice Guideline was developed using the RAND Corporation (RAND)/University of California, Los Angeles (UCLA) Appropriateness Method (RAM) – a process that combines scientific evidence and clinical knowledge to determine the appropriateness of a set of clinical procedures. The RAM is a deliberate approach encompassing review of existing guidelines, literature reviews, appropriateness ratings, necessity reviews, and document development. For this project, American Society of Addiction Medicine selected an independent committee to oversee guideline development and to assist in writing. American Society of Addiction Medicine's Quality Improvement Council oversaw the selection process for the independent development committee. Recommendations included in the guideline encompass a broad range of topics, starting with the initial evaluation of the patient, the selection of medications, the use of all the approved medications for opioid use disorder, combining psychosocial treatment with medications, the treatment of special populations, and the use of naloxone for the treatment of opioid overdose. Topics needing further research were noted.

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RATIONALE

Opioid use disorder is a chronic, relapsing disease, which has significant economic, personal, and public health consequences. This ''Practice Guideline'' was developed to assist in the evaluation and treatment of opioid use disorder. Although there are existing guidelines for the treatment of opioid use disorder, none have included all of the medications used at present for its treatment. 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. This article serves as an overview of the guideline. It is recommended that those who wish to understand this subject in sufficient detail to prescribe carefully should read the full guideline.

GUIDELINE FOCUS

This Practice Guideline was developed for the evaluation and treatment of opioid use disorder and for the management of opioid overdose. The medications covered in this guideline are mainly, but not exclusively, those that have been US Food and Drug Administration (FDA)-approved for the treatment of opioid dependence, as defined in prior versions of the Diagnostic and Statistical Manual (DSM) and not necessarily the current version of the manual, the DSM-5. 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. 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

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the use of those medications. As a final note, cost and/or cost effectiveness related to US FDA-approved or off-label medications were not considerations in the development of this Practice Guideline.

TARGET POPULATION

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.

GUIDELINE DEVELOPMENT PROCESS

This Practice Guideline was 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. The RAM is a deliberate approach encompassing review of existing guidelines, literature reviews, appropriateness ratings, necessity reviews, and document development. For this project, American Society of Addiction Medicine (ASAM) selected an independent committee to oversee guideline development, participate in review of treatment scenarios, and to assist in writing. ASAM's Quality Improvement Council, chaired by Margaret Jarvis, MD, oversaw the selection process for the independent development committee, referred to as the Guideline Committee.

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

EVIDENCE REVIEW AND GRADING

All existing clinical guidelines that addressed the use of medications and psychosocial treatments in the treatment of opioid use disorders, including special populations (eg, pregnant women, individuals with pain, and adolescents), and that were published during the period from January 2000 to April 2014, were identified and reviewed. In total, 49 guidelines were identified and 34 were ultimately included in the analysis. See Supplemental Digital Content 1, http://links.lww.com/JAM/A35 for a list of the guidelines that were reviewed. The included guidelines offered evidence-based recommendations for the treatment of opioid use disorder using methadone, buprenorphine, naltrexone, and/or naloxone.

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

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

Preparation of Literature Review on Psychosocial Interventions

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

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

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. Researchers included articles describing experimental or quasi-experimental trials examining the efficacy of medication for the treatment of opioid use disorder delivered in conjunction with a psychosocial intervention. Articles that were specific to a certain type of a population (eg, pregnant women or adolescents) were also included. Articles that did not include adequate control and that did not allow inference into the efficacy or incremental utility of delivering a psychosocial intervention in combination with medication-assisted treatment were excluded, as were studies with inadequate sample sizes (ie, less than 15 per group).

Further, researchers also excluded nonempirical articles such as commentaries and editorials. These articles, along with the relevant systematic reviews of the literature, are described in the literature review in the next section. A full article on the literature review will be published in a subsequent *JAM* edition.

RAND/UCLA Appropriateness Method

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

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

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

An appropriateness score of 1 meant that the statement was ''highly inappropriate.'' An appropriateness rating of 9 meant that the statement was ''highly appropriate.'' Consensus was defined as an average appropriateness rating of 7 or higher. These appropriateness statements were meant to identify a lack of consensus in existing guidelines and research literature.

Guideline Committee Meeting

Upon completion and collection of the individual Guideline Committee member ratings, 201 out of the 245 hypothetical statements were identified as meeting the criteria for consensus. The remaining 44 statements had divergent ratings. On September 15, 2014, the Guideline Committee met in Washington, District of Columbia, to discuss the hypothetical clinical statements. At this meeting, the committee came to consensus on the hypothetical statements. Additionally, the committee identified situations that occur regularly in clinical practice where scientific evidence is not available. Although there was not significant evidence, the committee felt strongly the need for recommendations. These are identified as committee consensus opinions. 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 was 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 as follows: urine drug testing; patients using marijuana; the safety of delivering injectable naltrexone doses every 3 weeks to patients who may rapidly metabolize naltrexone; and the safety of adding full agonists to treatment with buprenorphine for pain management.

After the appropriateness rating was complete, the hypothetical statements were re-rated for necessity. A statement was considered necessary if it would be considered improper care not to provide this service, a reasonable chance exists that this procedure and/or service will benefit the patient and the benefit to the patient is of significance and certainty. Of the 211 statements rated as appropriate, 184 hypothetical statements met the criteria for being both appropriate and necessary, and were incorporated into the guideline.

COMMENTS AND MODIFICATION

American Society of Addiction Medicine sought input from ASAM members, patient and caregiver groups, stakeholders including experts from the criminal justice system, government agencies, other professional societies, and hospitals and health systems. The invited reviewers had 3 weeks to review and provide comments. ASAM also made the document and a qualitative review guide available to ASAM members and the general public for a 1-week period of review and comment. The final draft Practice Guideline was submitted to the ASAM Board of Directors in April 2015. The Board of Directors made final comments which were reviewed by the Writing Committee, and the document was accepted in June 2015.

CLINICAL RECOMMENDATIONS

Part 1: Assessment and Diagnosis of Opioid Use Disorder

Assessment Recommendations

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.

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

A physical examination should be completed as a component of the comprehensive assessment process. The prescriber (the clinician authorizing the use of a medication for the treatment of opioid use disorder) may conduct this physical examination him/herself, or, in accordance with the ASAM Standards, ensure that a current physical

examination is contained within the patient medical record before a patient is started on a new medication for the treatment of his/her addiction.

The following laboratory tests may be necessary: complete blood count, liver function, hepatitis C, HIV and sexually transmitted infections, and TB. Hepatitis A and B testing and vaccination should be offered when appropriate. The assessment of females presents special considerations regarding their reproductive health. Women of childbearing age should be tested for pregnancy, and all women of childbearing potential and age should be queried regarding methods of contraception, given the increase in fertility that results from effective opioid use disorder treatment.

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

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

Concomitant use of alcohol and sedatives, hypnotics, or anxiolytics with opioids may contribute to respiratory depression. Patients with significant co-occurring substance use disorders, especially severe alcohol or sedative, hypnotic, or anxiolytic use, may require a higher level of care.

A tobacco use query and counseling on cessation of tobacco products should be completed routinely for all patients, including those who present for evaluation and treatment of opioid use disorder.

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

Diagnosis Recommendations

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

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.

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

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

Part 2: Treatment Options

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

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

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

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

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.

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

Part 3: Treating Opioid Withdrawal

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

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

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.

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

Opioid-dependent patients should wait until they are experiencing mild to moderate opioid withdrawal before taking the first dose of buprenorphine to reduce the risk of precipitated withdrawal.

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

The Guideline Committee recommends, based on consensus opinion, the inclusion of clonidine as a practice to support opioid withdrawal. Clonidine is not US FDA-approved for the treatment of opioid withdrawal, but it has been extensively used off-label for this purpose. Clonidine may be used orally or transdermally at doses of 0.1–0.3 mg every 6–8 hours, with a maximum dose of 1.2 mg daily to assist in the management of opioid withdrawal symptoms. There is a delay in response using transdermal clonidine that may require oral supplementation on day 1. Its hypotensive effects often limit the amount that can be used. Clonidine can be combined with other non-narcotic medications targeting specific opioid withdrawal symptoms such as benzodiazepines for anxiety, loperamide for diarrhea, acetaminophen or nonsteroidal anti-inflammatory medications (NSAIDs) for pain, and ondansetron or other agents for nausea.

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

Part 4: Methadone

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

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

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

The administration of methadone should be monitored because unsupervised administration can lead to misuse and diversion. OTP regulations require monitored medication administration until the patient's clinical response and behavior demonstrate that the prescribing of doses which are not monitored is appropriate.

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

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

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

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

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

Patients switching from methadone to oral naltrexone or extended-release injectable naltrexone must be completely withdrawn from methadone and other opioids, before they can receive naltrexone. This may take up to 14 days, and a naloxone challenge may be useful in determining the lack of physical dependence on opioids. 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.

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

Part 5: Buprenorphine

Opioid-dependent patients should wait until they are experiencing mild to moderate opioid withdrawal before taking the first dose of buprenorphine to reduce the risk of precipitated withdrawal.

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

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

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. Buprenorphine doses after induction and titration should be, on average, at least 8 mg per day. The US FDA approves dosing to a limit of 24 mg per day, and there is limited evidence regarding the relative efficacy of higher doses. In addition, the use of higher doses may increase the risk of diversion.

Psychosocial treatment should be implemented in conjunction with the use of buprenorphine in the treatment of opioid use disorder. This therapy may be provided by the prescribing clinician or by a separate therapist depending on the clinical situation and the skills and training of the prescribing clinician.

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

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

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

Buprenorphine taper and discontinuation is a slow process, indefinite in duration, and close monitoring should be done even after buprenorphine is stopped. Buprenorphine tapering is generally accomplished over several months. Patients should be encouraged to remain in treatment for ongoing monitoring past the point of discontinuation. When considering a switch from buprenorphine to naltrexone, 7–14 days should elapse between the last dose of buprenorphine and the start of naltrexone to ensure that the patient is not physically dependent on opioids before starting naltrexone. It may be useful to conduct a naloxone challenge before starting naltrexone to demonstrate an absence of physical dependence.

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

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

Part 6: Naltrexone

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

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

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

Psychosocial treatment is recommended in conjunction with treatment with oral and extended-release injectable naltrexone.

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

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

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

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

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

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.

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

Psychosocial treatment should be offered with oral and extended-release injectable naltrexone. The efficacy of extended-release injectable naltrexone to treat opioid use disorder has not been confirmed when it has been used as pharmacotherapy without accompanying psychosocial treatment.

Part 8: Special Populations: Pregnant Women

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.

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

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

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

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

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

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

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

Treatment with methadone or buprenorphine should be initiated as early as possible during pregnancy.

Hospitalization during initiation of methadone or buprenorphine may be advisable due to the potential for adverse events, especially in the third trimester.

In an inpatient setting, methadone should be initiated at a dose range of 20–30 mg, not to exceed 40 mg on day 1. Incremental doses of 5–10 mg are given every 3–6 hours, as needed, to treat withdrawal symptoms.

Initiation or induction of buprenorphine may lead to withdrawal symptoms in patients with physical dependence on opioids. To minimize this risk, induction should be initiated when a woman begins to show objective, observable signs of moderate withdrawal, but before severe withdrawal symptoms are evidenced. This usually occurs 6 hours or more after the last dose of a short-acting opioid, and typically 24–48 hours after the use of long-acting opioids. Hospitalization during initiation of treatment with buprenorphine may be advisable due to the potential for adverse events, especially in the third trimester. Drug dosing is similar to that in women who are not pregnant (see "Part 5: Buprenorphine" for more information).

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

Clinicians should be aware that the pharmacokinetics of methadone is affected by pregnancy. With advancing gestational age, plasma levels of methadone progressively decrease and clearance increases. Increased or split doses may be needed as pregnancy progresses. After child birth, doses may need to be adjusted. Twice-daily dosing is more effective and has fewer side effects than single dosing, but may not be practical because methadone is typically dispensed in an outpatient clinic.

Buprenorphine monoproduct is a reasonable and recommended alternative to methadone for pregnant women. The need to adjust dosing of buprenorphine during pregnancy is less than that of methadone. Clinicians may consider split dosing in patients who complain of discomfort and craving in the afternoon and evening. Whereas there is evidence of safety, there is insufficient evidence to recommend the combination buprenorphine/naloxone formulation.

Discontinuation of buprenorphine is not recommended before elective cesarean section as it creates the potential for fetal withdrawal.

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

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

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

Part 9: Special Populations: Individuals With Pain

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

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

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

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

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

Patients on methadone for the treatment of opioid use disorder and who are admitted for surgery may require additional short-acting opioid pain relievers. The dose of pain relievers prescribed may be higher than those required by the typical patient due to tolerance.

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

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

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

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

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

Part 10: Special Populations: Adolescents

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

Opioid agonists (methadone and buprenorphine) and antagonists (naltrexone) may be considered for treatment of opioid use disorder in adolescents. Age is a consideration in treatment, and federal laws and US FDA approvals need to be considered for patients under the age 18. Buprenorphine is US FDA-approved for adolescents aged 16 years and above.

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

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

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

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

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

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

All patients with psychiatric disorders should be asked about suicidal ideation and behavior. Patients with a history of suicidal ideation or attempts should have opioid use disorder medications and psychiatric medications monitored more carefully.

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

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

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

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

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

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

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

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

Part 13: Naloxone for the Treatment of Opioid Overdose

Naloxone should be given in case of opioid overdose.

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

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

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

RESEARCH RECOMMENDATIONS

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

Assessment and Diagnosis of Opioid Use Disorder (Part 1)

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

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

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

Treatment Options (Part 2)

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

Opioid Withdrawal Management (Part 3)

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

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

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

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

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

Methadone (Part 4)

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

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

Buprenorphine (Part 5)

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

Naltrexone (Part 6)

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

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

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

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

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

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

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

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

Special Populations: Pregnant Women (Part 8)

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

Special Population: Individuals With Pain (Part 9)

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

Special Populations: Adolescents (Part 10)

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

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

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

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

APPLICABILITY AND IMPLEMENTATION ISSUES

This Guideline is intended to aid decision-making in the treatment of opioid-addicted patients. This is not a set of standards, and there will likely be situations in which physicians consciously decide not to follow the recommendations of the Guideline for reasons that are applicable to individual patients. The Guideline was written to be used by physicians who are experienced in the treatment of addicted patients, and by those who are not so experienced. Any physician using the Guideline must be aware of her/his capabilities, and judge when a stricter interpretation of the Guideline, or a referral to a more experienced practitioner would be indicated.

CONCLUSIONS

At this point in time, the available evidence indicates that use of medications in addition to psychosocial treatments is supported for the treatment of opioid use disorder. Prescription of the indicated medications is not completely simple, and skill and time are required to ensure that treatment is effective and diversion of the abusable medications is not occurring. This Guideline describes aspects of treatment that should be attended to be effective.

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Key References and Disclosures

All references and disclosures are included in the full guideline (see Supplemental Digital Content 1, http://links.lww.com/JAM/A35).