VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF SUBSTANCE USE DISORDERS

Department of Veterans Affairs

Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs and the Department of Defense guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

This Clinical Practice Guideline is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendation.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

These guidelines are not intended to represent TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

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I. Introduction

The Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Work Group (EBPWG) was established and first chartered in 2004, with a mission to advise the "…Health Executive Council on the use of clinical and epidemiological evidence to improve the health of the population across the Veterans Health Administration and Military Health System," by facilitating the development of clinical practice guidelines (CPGs) for the VA and DoD populations.[1] This CPG is intended to provide healthcare providers with a framework by which to evaluate, treat, and manage the individual needs and preferences of patients with substance use disorders (SUD), thereby leading to improved clinical outcomes.

In 2009, the VA and DoD published a CPG for the Management of Substance Use Disorders (2009 SUD CPG), which was based on evidence reviewed through 2007. Since the release of that guideline, a growing body of research has expanded the general knowledge and understanding of SUD. Improved recognition of the complex nature of these conditions has led to the adoption of new strategies to manage and treat patients with SUD, including new developments related to pharmacotherapy and other treatment options.

Consequently, a recommendation to update the 2009 SUD CPG was initiated in 2014. The updated CPG includes objective, evidence-based information on the management of SUD. It is intended to assist healthcare providers in all aspects of patient care, including, but not limited to, diagnosis, treatment, and follow-up. The system-wide goal of evidence-based guidelines is to improve the patient's health and wellbeing by guiding health providers who are taking care of patients with SUD along the management pathways that are supported by evidence. The expected outcome of successful implementation of this guideline is to:

- Assess the patient's condition and determine in collaboration with the patient the best treatment method
- Optimize each individual's recovery to decrease or eliminate consumption, improve health and wellness, live a self-directed life, and strive to reach his or her full potential [2]
- Minimize preventable complications and morbidity
- Emphasize the use of patient-centered care

II. Background

A. Description of Substance Use Disorders

SUD can develop in individuals who use alcohol or other addicting drugs in harmful quantities. About 9% of Americans over age 18 have a non-tobacco SUD, and about one in every four Americans will develop a non-tobacco SUD over the course of a lifetime.[3,4] According to the Centers for Disease Control and Prevention (CDC), excessive alcohol use costs the United States (U.S.) over $223.5 billion annually.[5] According to the U.S. Department of Justice, the estimated cost of illicit drug use in the U.S. was more than $193 billion (in 2007).[6] This reflects direct and indirect public costs related to crime ($61.4 billion), health ($11.4 billion), and lost productivity ($120.3 billion).[6] Excessive alcohol use itself leads to about 88,000 premature deaths each year from acute (e.g., alcohol poisoning, motor vehicle accidents) and chronic causes (e.g., liver disease, hypertension, heart disease, stroke, pancreatitis). SUDs including tobacco

represent the leading actual cause of death in the U.S.[7] While the costs to our nation's health are high, healthcare professionals are in a unique position to positively impact the health and wellbeing of the Service Members and Veterans they treat by implementing effective SUD prevention and treatment strategies.

As termed in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a "substance use disorder describes a problematic pattern of using alcohol or another substance that results in impairment in daily life or noticeable distress."[8] This use can lead to a change in the way the brain functions and can cause other long-term health problems such as cardiovascular disease, stroke, and lung disease.[9] It can also limit a person's ability to fulfill roles in his or her professional or personal life and can have other legal, social, or physical ramifications.[10,11]

In the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (and in International Classification of Diseases, Tenth Revision), SUD consists of two distinct conditions, abuse and dependence, as they relate to substances such as tobacco, alcohol, opioids, cannabis, and seven others. Field trials of the DSM-IV criteria showed that the substance dependence syndrome was both reliable and valid as a definition, but that the abuse syndrome based on a theoretical and hierarchical relationship between abuse (less severe) and dependence (more severe) was not valid. Some symptoms of "abuse" (e.g., failure to fulfill major role obligations) indicated severe SUD, while about half of the "abuse" definitions were based only on a single criterion, most often "hazardous use."[12] Factor analysis supports a single SUD syndrome. Thus, DSM-5 now defines SUD using 11 diagnostic criteria and defines mild, moderate, and severe sub-classifications.[8] Presence of at least two symptoms indicates a disorder. Severity is defined as mild, moderate, and severe, with the presence of two to three, four to five, and six or more symptoms, respectively.[8,12]

Addictive substances disrupt the functioning of brain circuits that mediate a complex array of functions (e.g., motivation, decision making, memory) involved in obtaining the natural rewards such as food and water that are essential for survival. Addicting substances act by either mimicking the brain's natural chemicals or by interfering with the brain's regulation of its chemicals, or both.[13] This activity changes the reward system in patients with SUD. When functioning normally, the mesolimbic dopamine pathway allows a person to experience pleasure in response to stimuli such as food and social interactions, and therefore encourages and motivates an individual to seek out these stimuli. Connections between mesolimbic dopamine and memory circuits enable a person to remember the people, places, and things associated with the reward. Addicting substances activate mesolimbic dopamine pathways more powerfully than natural rewards. With sufficient repeated use of addicting substances, one can develop an SUD. In patients with SUD, the mesolimbic pathway responds to cues that addictive substances are available, while its response to the drug itself and to natural rewards diminishes. Simultaneously, repeated substance use impairs the ability to exert inhibitory control. Over time, substance-related cues become more salient, drug craving becomes more compelling, and the individual is less able to inhibit impulses to use substances even as the "high" experienced is diminished.[14] This leads to impairment in substance-related decision making that leads to many of the DSM-5 symptoms of an SUD.

B. Epidemiology and Impact

In 2014, an estimated 8.1% of the population indicated they were affected by SUD within the past year. An estimated 6.4% were affected by alcohol use disorder (AUD), while 2.7% were affected by an illicit drug use disorder.[15] The leading causes of death in 2000 were tobacco (435,000 deaths; 18.1% of total U.S. deaths), poor diet and physical inactivity (365,000 deaths; 15.2%), and alcohol consumption (85,000 deaths; 3.5%). Other causes of death were microbial agents (75,000), toxic agents (55,000), motor vehicle crashes (43,000), incidents involving firearms (29,000), sexual behaviors (20,000), and illicit use of drugs (17,000).[7] From 1990-2010, the highest disability-adjusted life years, which accounted for years of life lost due to premature mortality as well as years lived with disability, were associated with risk factors including dietary risks, tobacco smoking, high body mass index, high blood pressure, high fasting plasma glucose, physical inactivity, and alcohol use.[16] Since the early 1990s, there has been an increase in marijuana and prescription drug use disorders.[17] During a similar time period (1999-2008), overall opioid related death rates also increased. [18] Deaths from opioid overdose more than tripled between 1999 and 2012.[19] Following the rise in prescription opioid use, heroin use increased from 2002 to 2013, and deaths resulting from heroin overdose also concurrently increased.[20]

Despite the increases in both use of many of these substances and associated mortality, alcohol and drug use disorders continue to be undertreated.[17,21] From the 2012-2013 National Epidemiologic Survey on Alcohol and Related Conditions III (NESARC-III), only 19.8% of respondents with lifetime AUD were ever treated for AUD.[21] Many individuals who are untreated identify stigma as a major barrier.[22,23]

For treatment of alcohol or illicit drug use in 2013, the most common locations of treatment were outpatient rehabilitation facilities or mutual help groups.[24,25] Among Gulf War, Afghanistan, and Iraq War era Veterans, Veterans who were deployed were found to be at increased risk of AUD compared to Veterans who were not deployed.[26]

C. Factors Affecting Risk of Substance Use Disorders

The risk of a person developing SUD is affected by a number of factors. One factor is biology, including genetic make-up, gender, ethnicity, and the presence of other comorbidities. For instance, rates of alcohol and drug use disorders in males are nearly double that in females.[27] In 2012-2013, 12-month and lifetime prevalence of AUD were higher for people who identified as white and Native American.[21] There is an increased risk for developing substance and other mental health disorders if a relative is affected by SUD.[27] Other factors that may affect development of the disease are social environment and age or stage of development. As adolescents' brains are still developing, including areas governing decision making and self-control, they may be more susceptible to taking risks such as using alcohol or drugs. The prevalence of alcohol and drug use disorders peaks in late adolescence and early adulthood, and starts to decrease after age 26.[27] In addition, those who were affected by substance use earlier in their lives are more likely to be affected by SUD in adulthood.[28] Socioeconomic status, SUD in family and friends, and quality of life can also influence risk.[29]

D. Substance Use Disorders in the Department of Veterans Affairs and the Department of Defense

SUD commonly co-occurs with and complicates other conditions or issues. These conditions or issues may be health-related, such as other mental health conditions, or may be societal, such as homelessness,

criminal justice involvement, or unemployment. For instance, among Veterans with posttraumatic stress disorder (PTSD), co-occurring SUD was common and found to be associated with an increase in mortality. The association was especially pronounced for young Veterans, including those who served in Iraq and Afghanistan.[30] Furthermore, it was found that roughly 33% and 22% of homeless Veterans had spent money on alcohol and drugs, respectively, in the past month; however, there was no significant association found between the source of income (e.g., VA disability compensation) and the amount spent on alcohol and drugs.[31] Among Iraq or Afghanistan Veterans who were first-time users of VA healthcare between October 15, 2001 and September 30, 2009 and followed through January 1, 2010, SUD diagnoses were associated with being male, less than 25 years of age, and exposed to combat.[32] Of those with an SUD diagnosis, 55-75% also received diagnoses for PTSD or depression.[32]

E. Working Toward Successful Substance Use Disorders Treatment

It is common for a person to relapse, even if his or her condition is being managed, and he or she is amenable to treatment. Relapse does not indicate that treatment has failed, but only signals that it needs to be adjusted, reinstated, or changed in order to move toward recovery.[33]

III. About this Clinical Practice Guideline

This guideline represents a significant step toward improving the treatment and management of patients with SUD in the VA and DoD. As with other CPGs, however, challenges remain, including evidence gaps, the need to develop effective strategies for guideline implementation and to evaluate the effect of guideline adherence on clinical outcomes. This guideline is intended for VA and DoD healthcare practitioners including physicians, nurse practitioners, physician assistants, psychologists, social workers, nurses, pharmacists, chaplains, addiction counselors, and others involved in the care of Service Members or Veterans who have a suspected or diagnosed SUD.

As elaborated in the qualifying statement on page one, this CPG is not intended to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and patterns evolve. This CPG is based on information available by January 2015 and is intended to provide a general guide to best practices. The guideline can assist care providers, but the use of a CPG must always be considered as a recommendation, within the context of a provider's clinical judgment and patient values and preferences, for the care of an individual patient.

A. Methods

The current document is an update to the 2009 VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. The methodology used in developing the 2015 CPG follows the *Guideline for Guidelines*,[1] an internal document of the VA and DoD EBPWG. The *Guideline for Guidelines* can be downloaded from http://www.healthquality.va.gov/policy/index.asp. This document provides information regarding the process of developing guidelines, including the identification and assembly of the Guideline Champions (Champions) and other subject matter experts from within the VA and DoD, known as the Work Group, and ultimately, the development and submission of a new or updated SUD CPG.

The Champions and Work Group for this CPG were charged with developing evidence-based clinical practice recommendations and writing and publishing a guideline document to be used by providers within the VA/DoD healthcare systems. Specifically, the Champions and Work Group members for this guideline were responsible for identifying the key questions (KQs) of the most clinical relevance, importance, and interest for the management of patients with SUD. The Champions and the Work Group also provided direction on inclusion and exclusion criteria for the evidence review and assessed the level and quality of the evidence. The amount of new scientific evidence that had accumulated since the previous version of the CPG was also taken into consideration in the identification of the KQs. In addition, the Champions assisted in:

- Identifying appropriate disciplines of individuals to be included as part of the Work Group
- Directing and coordinating the Work Group
- Participating throughout the guideline development and review processes

The VA Office of Quality, Safety and Value, in collaboration with the Office of Evidence Based Practice, U.S. Army Medical Command, the proponent for CPGs for the DoD, identified three clinical leaders, Karen Drexler, MD and Daniel Kivlahan, PhD from the VA and Lieutenant Colonel Christopher Perry, MD from the DoD, as Champions for the 2015 CPG.

The Lewin Team, including The Lewin Group, Duty First Consulting, ECRI Institute, and Sigma Health Consulting, LLC, was contracted by the VA and DoD to support the development of this CPG and conduct the evidence review. The first conference call was held in October 2014, with participation from the contracting officer's representative (COR), leaders from the VA Office of Quality, Safety and Value and the DoD Office of Evidence Based Practice, and the Champions. During this call, participants discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing and prioritizing specific research questions on which to base a systematic review (SR) about the management of SUD. The group also identified a list of clinical specialties and areas of expertise that are important and relevant to the management of SUD, from which Work Group members were recruited. The specialties and clinical areas of interest included: psychiatry, psychology, nursing, pharmacy, social work, primary care, family medicine, religious and spiritual services, bioethics, dietetics, pain, addiction psychiatry, addiction medicine, and substance use specialties.

The guideline development process for the 2015 CPG update consisted of the following steps:

1. Formulating and prioritizing evidence questions (KQs)
2. Conducting the SR
3. Convening a face-to-face meeting with the CPG Champions and Work Group members
4. Drafting and submitting a final CPG about the management of SUD to the VA/DoD EBPWG

Appendix A provides a detailed description of each of these tasks.

a. Grading Recommendations

The Champions and Work Group used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of the evidence base and assign a grade for the strength

for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation:[34]

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Patient or provider values and preferences
- Other implications, as appropriate, e.g.,:
    - Resource use
    - Equity
    - Acceptability
    - Feasibility
    - Subgroup considerations

Using this system, the Champions and Work Group determined the relative strength of each recommendation (Strong or Weak). A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they give a weak recommendation.

They also determined the direction of each recommendation (For or Against). Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong For (or "We recommend offering this option …")
- Weak For (or "We suggest offering this option …")
- Weak Against (or "We suggest not offering this option …")
- Strong Against (or "We recommend against offering this option …")

The grade of each recommendation made in the 2015 CPG can be found in the section on Recommendations. Additional information regarding the use of the GRADE system can be found in Appendix A.

b. Reconciling 2009 Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current, which typically requires revisions of previous guidelines based on new evidence, or as scheduled, subject to time-based expirations.[35] For example, the U.S. Preventive Services Task Force (USPSTF) has a process for refining or otherwise updating its recommendations pertaining to preventive services.[36] Further, the inclusion criteria for the National Guideline Clearinghouse specify that a guideline must have been developed, reviewed, or revised within the past five years.

The SUD Guideline Work Group focused largely on developing new and updated recommendations based on the evidence review conducted for the priority areas addressed by the KQs. In addition to those new and updated recommendations, the Guideline Work Group considered, without complete review of the relevant evidence, the current applicability of other recommendations that were included in the previous 2009 SUD CPG, subject to evolving practice in today's environment.

A set of recommendation categories was adapted from those used by the National Institute for Health and Care Excellence (NICE).[37,38] These categories, along with their corresponding definitions, were used to account for the various ways in which older recommendations could have been updated. In brief, the categories took into account whether or not the evidence that related to a recommendation was systematically reviewed, the degree to which the recommendation was modified, and the degree to which a recommendation is relevant in the current patient care environment and inside the scope of the CPG. Additional information regarding these categories and their definitions can be found in Appendix A. The categories for the recommendations included in the 2015 version of the guideline can be found in the section on Recommendations. The categories for the recommendations from the 2009 SUD CPG are noted in Appendix E.

The CPG Work Group recognized the need to accommodate the transition in evidence rating systems from the 2009 SUD CPG to the current CPG. In order to report the strength of all recommendations using a consistent format (i.e., the GRADE system) the CPG Work Group converted the USPSTF strengths of the recommendation accompanying the carryover recommendations from the 2009 guideline to the GRADE system. As such, the CPG Work Group considered the strength of the evidence cited for each recommendation in the 2009 SUD CPG as well as harms and benefits, values and preferences, and other implications, where possible. The CPG Work Group referred to the available evidence as summarized in the body of the 2009 SUD CPG and did not re-assess the evidence systematically. In some instances, peer-reviewed literature published since the 2009 SUD CPG was considered along with the evidence base used for that CPG.

Where such newer literature was considered when converting the strength of the recommendation from the USPSTF to the GRADE system, it is referenced in the discussion that follows the corresponding recommendation, as well as in Appendix D.

The CPG Work Group recognizes that, while there are practical reasons for incorporating findings from a previous SR, previous recommendations,[39] or recent peer-reviewed publications into an updated CPG, doing so does not involve an original, comprehensive SR and, therefore, may introduce bias.

c. Peer Review Process

The CPG was developed through an iterative process in which the Work Group produced multiple drafts of the CPG. The process for developing the initial draft is described in more detail in Drafting and Submitting the Final Clinical Practice Guideline.

Once a near-final draft of the guideline was agreed upon by the Champions and Work Group members, the draft was sent out for peer review and comment. The draft was posted on a wiki website for a period of 14 business days. The peer reviewers comprised individuals working within the VA and DoD health systems as well as experts from relevant outside organizations designated by the Work Group members.

Organizations designated by the Work Group who were contacted to participate in the peer review included the following:

- American Psychiatric Nurses Association, Addictions Council
- International Nurses Society on Addictions
- Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment

The VA and DoD Leadership reached out to both the internal and external peer reviewers to solicit their feedback on the CPG. Reviewers were provided a hyperlink to the wiki website where the draft CPG was posted. All reviewer feedback was posted in tabular form on the wiki site, along with the name of the reviewer, for transparency. All feedback from the peer reviewers was discussed and considered by the Work Group. Modifications made throughout the CPG development process were made in accordance with the evidence.

B. Conflict of Interest

At the start of this guideline development process and at other key points throughout, the project team was required to submit disclosure statements to reveal any areas of potential conflict of interest (COI) in the past 12 months. Verbal affirmations of no COI were used as necessary during meetings throughout the guideline development process. The project team was also subject to random web-based surveillance (e.g., ProPublica). Disclosed industry related COIs are listed in Appendix G.

If a project team member reported a COI (actual or potential), then it was reported to the Office of Evidence Based Practice. It was also discussed with the SUD CPG Work Group in tandem with their review of the evidence and development of recommendations. The Office of Evidence Based Practice and the SUD CPG Work Group determined whether or not action, such as restricting participation and/or voting on sections related to the conflict or removal from the Work Group, was necessary. If it was deemed necessary, action was taken by the co-chairs and Office of Evidence Based Practice, based on the level and extent of involvement, to mitigate the COI.

Several Work Group members disclosed relationships and/or affiliations which had the potential to introduce bias into the guideline. Based on the level and extent of involvement, no individuals were removed from the Work Group. In order to mitigate the risk of bias while maximizing the contributions of those with expertise in a specific area of SUD treatment, co-chairs asked Work Group members to disclose relevant relationships during related guideline development discussions. Members with potential COIs contributed to the discussions related to their particular areas of expertise as well as the overarching guideline document in order to ensure differing viewpoints and experiences were adequately represented.

C. Scope of this Clinical Practice Guideline

Regardless of setting, any patient in the healthcare system should be offered access to the interventions that are recommended in this guideline after taking into consideration the patient's specific circumstances.

Guideline recommendations are intended to be patient-centered. Thus, treatment and care should take into account a patient's needs and preferences. Good communication between healthcare professionals and the patient is essential and should be supported by evidence-based information tailored to the

patient's needs. Use of an empathetic and non-judgmental (versus a confrontational) approach facilitates discussions sensitive to gender, culture, and ethnic differences. The information that patients are given about treatment and care should be culturally appropriate and also available to people with limited literacy skills. It should also be accessible to people with additional needs such as physical, sensory, or learning disabilities. Family involvement should be considered if appropriate.

This CPG is designed to assist providers in managing or co-managing patients with SUD. Moreover, the patient population of interest for this CPG is adults who are eligible for care in the VA and DoD healthcare delivery systems. It includes Veterans as well as deployed and non-deployed Active Duty Service Members. This CPG does not provide recommendations for the management of SUD in children or adolescents.

The literature review encompassed interventional studies (primarily randomized controlled trials [RCTs]) published between November 2007 and January 2015, and targeted 12 KQs focusing on the means by which the delivery of healthcare could be optimized for patients with SUD. The selected KQs were prioritized from many possible KQs. Due to resource constraints, a review of the evidence in all important aspects of care for patients with SUD was not feasible for the update to this CPG.

D. Highlighted Features of this Clinical Practice Guideline

The 2015 edition of the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders is the second update to the original CPG. It provides practice recommendations for the care of populations with SUD with any level of severity. While screening for and addressing co-occurring mental disorders is considered good clinical practice, specific guidance on management of co-occurring mental health conditions and SUD is beyond the scope of this CPG. Interested readers are referred to related VA-DoD CPGs (see Substance Use Disorders and Co-occurring Conditions). A particular strength of this CPG is the multidisciplinary stakeholder involvement from its inception, ensuring representation from the broad spectrum of clinicians engaged in the treatment and management of patients with SUD.

The framework for recommendations in this CPG considered factors beyond the strength of the evidence, including balancing desired outcomes with potential harms of treatment, equity of resource availability, and the potential for variation in patient values and preferences. Applicability of the evidence to VA/DoD populations was also taken into consideration. A structured algorithm accompanies the guideline to provide an overview of the recommendations in the context of the flow of patient care and clinician decision making and to assist with training providers. The algorithm may be used to help facilitate translation of guideline recommendations into effective practice.

E. Patient-centered Care

VA/DoD CPGs encourage clinicians to use a patient-centered care approach that is individualized based on patient capabilities, needs, goals, prior treatment experience and preferences. Regardless of setting, all patients in the healthcare system should be offered access to evidence-based interventions appropriate to that patient. When properly executed, PCC may decrease patient anxiety, increase trust in clinicians,[40] and improve treatment adherence.[41] Improved patient-clinician communication through PCC can be used to convey openness to discuss any future concerns.

As part of the PCC approach, clinicians should review the outcomes of previous self-change efforts, past treatment experiences, and outcomes (including reasons for treatment drop-out) with the patient. They

should ask the patient about willingness to accept a referral to an addiction specialist. Lastly, they should involve the patient in prioritizing problems to be addressed and in setting specific goals regardless of the selected setting or level of care.

F. Shared Decision Making

Throughout this VA/DoD CPG, the authors encourage clinicians to focus on shared decision making (SDM). The SDM model was introduced in *Crossing the Quality Chasm,* an Institute of Medicine report, in 2001.[42] It is readily apparent that patients with SUD, together with their clinicians, make decisions regarding which care they choose to engage in; however, these patients require sufficient information to be able to make informed decisions. Clinicians must be adept at presenting information to their patients regarding both individual treatments and levels and locations of care. For instance, for a patient who is not interested in specialty referral, the clinician should briefly explore the patient's rationale, present relevant and individualized information about how specialty care might better meet the patient's needs, identify reasons a specialty referral might be recommended for his or her specific case, and provide information regarding the abilities and the limitations of the primary care or general mental health clinic. If the patient continues to decline specialty referral despite counseling, the primary care clinician should respect this decision by providing as much care as possible for the patient. Unfortunately, SDM can be complicated as the patients' ability to make decisions may be impaired by the SUD itself.[43]

G. Engagement Strategies

A fundamental goal of this VA/DoD CPG is to promote early engagement and retention of patients with substance use conditions who can benefit from addiction-focused treatment. Many patients may initially decline voluntary referral,[44] or at least express ambivalence, but provider encouragement and support may improve patient willingness to pursue further involvement if they see it as consistent with their other priorities. There is considerable evidence from psychotherapy research that general factors such as therapist skill, the strength of the therapeutic alliance, and the structure provided by regular clinical contact can have as powerful an effect on engagement as the specific content or conceptual approach of specialized interventions.[45] Therefore, attention to these general therapeutic factors is at least as important as the specific treatment approach selected.

The following principles are fundamental to the engagement/re-engagement process for patients with SUD:

1. Indicate to the patient and significant others that treatment is more effective than no treatment (i.e., "Treatment works").
2. Consider the patient's prior treatment experience and respect patient preference for the initial intervention approach(es), since no single intervention approach has emerged as the treatment of choice.
3. Regardless of the particular psychosocial intervention chosen, use motivational interviewing (MI) style during therapeutic encounters with patients [46-48] and emphasize the common elements of effective interventions including: improving self-efficacy for change, promoting a therapeutic relationship, strengthening coping skills, changing reinforcement contingencies for recovery, and enhancing social support for recovery.

4. Emphasize that the most consistent predictors of successful outcome are retention in formal treatment and/or active involvement with community support for recovery.
5. Use strategies demonstrated to be efficacious to promote active involvement in available mutual help programs (e.g., Alcoholics Anonymous [AA], Narcotics Anonymous [NA]).
6. Coordinate addiction-focused psychosocial interventions with evidence-based intervention(s) for other biopsychosocial problems to address identified concurrent problems consistent with patient priorities.
7. Provide intervention in the least restrictive setting necessary to promote access to care, safety and effectiveness.
8. If a patient drops out of treatment, the treatment team should make efforts to contact the patient and re-engage him/her in treatment.
9. If the patient remains unwilling to engage in any addiction-focused care, maintain MI style of interactions. Emphasize that options remain available in the future and determine whether treatment for medical and psychiatric problems can be effectively and safely provided while looking for windows of opportunity to engage the patient in addiction treatment.

Even when patients refuse referral or are unable to participate in specialized addiction treatment, many are accepting of general medical or mental health care. The chronic illness approach is consistent with management approaches for many other disorders treated in medical and psychiatric settings.[33,49]

H. Addiction-focused Medical Management

Addiction-focused Medical Management is a manualized psychosocial intervention designed to be delivered by a medical professional (e.g., physician, nurse, physician assistant) in a primary care setting.[50] The treatment provides strategies to increase medication adherence and monitoring of substance use and consequences, as well as supporting abstinence through education and referral to support groups.

While variably defined, addiction-focused Medical Management typically includes:[51-55]

1. Monitoring self-reported use, laboratory markers, and consequences
2. Monitoring adherence, response to treatment, and adverse effects
3. Education about AUD and/or OUD consequences and treatments
4. Encouragement to abstain from non-prescribed opioids and other addictive substances
5. Encouragement to attend community supports for recovery (e.g., mutual help groups) and to make lifestyle changes that support recovery

Session structure varies according to the patient's substance use status and treatment compliance. An initial session (40-60 minutes) may involve discussion of the specific findings and diagnosis, negative consequences from substance use, a recommendation to abstain, medication information, strategies to enhance medication adherence, and referral to support groups. In the subsequent monitoring visits, the clinician assesses the patient's substance use. The assessment includes monitoring lab or physiologic measures and assessing overall functioning, medication adherence, and any medication side effects.

Follow-up sessions are typically 15-20 minutes initially twice weekly tapering to weekly then biweekly for up to 12 weeks. When the patient does not adhere to the medication regimen, the clinician evaluates the reasons and helps the patient devise plans to address the problem(s). Clinicians offer common sense recommendations, such as avoiding specific situations like going to bars. If the patient suffers from medication side effects, the clinician specifies procedures for using concomitant medication to ameliorate them or reduces the dosage of medication, resuming medications if side effects remit. If a patient discontinues medication because he or she cannot tolerate it, the clinician schedules a monthly 15- to 25-minute "medical attention" meeting, during which the clinician employs a similar approach that focuses on the patient's substance use and overall health, omitting the medication adherence component.

I. Accreditation Standards

This VA/DoD CPG was developed with a focus on evidence-based practices to help improve patient outcomes. Although they are not explicitly evidence-based, attention should be given to standards provided by various accrediting agencies, most notably The Joint Commission (TJC) and the Commission on Accreditation of Rehabilitation Facilities (CARF). TJC standards can be found at: http://www.jointcommission.org/standards_information/standards.aspx. CARF standards can be found at: http://www.carf.org/home/.

TJC accreditation requirements address important functions relating to the care, treatment, or services of individuals and the management of behavioral health care organizations. They provide a framework to help manage risk and enhance the quality and safety of care, treatment, and services. For many providers and organizations, including VA and DoD, these requirements are considered to be the standard of care.

The mission of CARF is to promote the quality, value, and optimal outcomes of services through a consultative accreditation process and continuous improvement services that center on enhancing the lives of persons served.

Among the accreditation standards, clinicians are expected to obtain a comprehensive biopsychosocial assessment with a diagnostic formulation that synthesizes the various assessments and, using the results from the assessment, to develop an individualized treatment plan in accordance with TJC or CARF standards.

J. Management of Substance Use Disorders in Department of Defense Healthcare Settings

As specified by the DoD, "Substance abuse[1] by military personnel is inconsistent with the Department of Defense's Values, the Warrior Ethos, and the standards of performance, discipline, and readiness necessary to accomplish the DoD's mission."[56] On 28 September 1971, Public Law (PL) 92-129, mandated that the Secretary of Defense develop programs for the identification, treatment, and

[1] Although the terminology "substance abuse" is not a diagnostic term and is not used elsewhere in the CPG, it is the language used in DoD policy and is thus used in this section.

rehabilitation of alcohol or other substance dependent persons in the Armed Forces.[57] In turn, the Secretary of Defense requires each of the Services to develop alcohol and other substance abuse prevention and control programs in accordance with Department of Defense Directive (DODD) 1010.4.[58] In response to these directives, the DoD conducts a comprehensive program to prevent and control the abuse of alcohol and other substances. The service specific programs are designed to strengthen the overall fitness and effectiveness of the DoD workforce, conserve manpower, enhance combat readiness, and increase individual fitness and overall unit readiness.

The DoD substance abuse programs are command and medical programs that emphasize readiness and personal responsibility. These programs are designed to provide services which are proactive and responsive to the needs of the DoD workforce by emphasizing alcohol and other substance abuse deterrence, prevention, education, and rehabilitation. The implementation of alcohol and other substance risk reduction and prevention strategies are designed to provide effective alcohol and other substance abuse prevention and education at all levels of command, and encourage commanders to provide alcohol and drug-free leisure activities. The ultimate goal of DoD substance use programs is to improve readiness and to restore to duty those substance-impaired Service Members who have the potential for continued military service.

In the DoD, Active Duty Service Members who are involved in the abuse of alcohol or use of illicit substances are encouraged to voluntarily refer themselves for care and treatment to a substance use program. However, if a Service Member screens positive for the use of illicit drugs during a mandatory unit urinalysis, regulations require that the Service Member enroll into a substance abuse program and be processed for possible separation from the military. The Service Member's commander intervenes early for all personnel assigned to his/her command suspected of being alcohol and/or substance abusers. Service Members, who fail to participate adequately in substance use programs or to respond successfully to rehabilitation, may be faced with administrative separation from the military.

After enrollment into substance abuse programs, all Active Duty Service Members will have a treatment team convene with the patient, clinician, and command representative to review the treatment plan and goals. Recognizing the importance of medical readiness, the Health Insurance Portability and Accountability Act (HIPAA) specifically exempts some communication between clinicians and commanders. Regulations require that Active Duty personnel enrolled in rehabilitation and referral services have an individualized aftercare plan designed to identify the continued support of the patient with monthly monitoring (minimally) during the first year after inpatient treatment. The following regulations guide the rehabilitation programs in the various services: Army Regulation 600-85, The Army Substance Abuse Program dated 28 Dec 2012;[56] OPNAVINST 5350.4D, Navy Alcohol and Drug Abuse Prevention and Control dated 04 Jun 2009;[59] Air Force Instruction 44-121, Alcohol and Drug Abuse Prevention and Treatment (ADAPT) dated 08 July 2014.[60]

Care of Veterans and Service Members in transition between facilities, services, or from the DoD healthcare system to the VA healthcare system should include a transition plan that ensures continuity of care and coordination among providers. Healthcare teams should work jointly to provide assessment and services to patients within this transitioning population. Management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

If a clear transition process is lacking, then an effort should be made to construct a functional transition process that supports PCC.

K. Substance Use Disorders and Co-occurring Conditions

a. Substance Use Disorder and Tobacco Use

In *Combatting Tobacco Use in Military and Veteran Populations*, the Institute of Medicine (2009) notes that great progress has been made in decreasing the rate of smoking of Active Duty and Veterans from 51% in 1980 to 32% in 2005, but that about 22% of Veterans enrolled in VA healthcare continue to smoke.[61] In its discussion about tobacco use disorder treatment during SUD treatment the Substance Abuse and Mental Health Services Administration (SAMHSA) (2011) notes an early study on the morbidity and mortality among people seeking treatment for addictions.[62] Among the 845 participants in that study, 51% died as a result of tobacco-related causes rather than from other substance-related causes.[63]

Quitting tobacco use has clear benefits for improving ongoing health and decreasing mortality and is strongly encouraged for all patients with SUD. Consistently offering tobacco use disorder treatment throughout SUD treatment supports the principles of PCC, shared decision making (SDM), and recovery. For management of tobacco use disorder, refer to the CPG: Treating Tobacco Use & Dependence: 2008 Update from the U.S. Department of Health and Human Services, available at: http://bphc.hrsa.gov/buckets/treatingtobacco.pdf; VA/DoD Clinical Practice Guideline for the Management of Tobacco Use, available at: http://www.healthquality.va.gov/guidelines/cd/mtu/index.asp; and the USPSTF Final Recommendation Statement Behavioral and Pharmacotherapy Interventions for Tobacco Smoking Cessation in Adults and Pregnant Women, available at: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions1.

b. Patients with Multiple Substance Use Disorders

Patients with more than one SUD should be managed according to the recommendations made for each of those individual disorders.

c. Substance Use Disorder and Other Co-occurring Conditions

For management of patients presenting with SUD and one or more of the following conditions, refer to the appropriate VA/DoD CPG, as available, at http://www.healthquality.va.gov/:

- Bipolar disorder
- Chronic Kidney Disease (CKD)
- Chronic Multisymptom Illness (CMI)
- Diabetes
- Hypertension
- Low Back Pain
- Major Depressive Disorder (MDD)
- Mild Traumatic Brain Injury (mTBI)

- PTSD
- Chronic Opioid Therapy
- Suicide

L. Implementation

This CPG and algorithm are designed to be adapted by individual healthcare providers with consideration of local needs and resources. The algorithms serve as a tool to prompt providers to consider key decision points in the course of an episode of care.

Although this CPG represents the recommended practice on the date of its publication, medical practice is evolving and this evolution requires continuous updating based on published information. New technology and more research will improve patient care in the future. The CPG can assist in identifying priority areas for research and to inform optimal allocation of resources. Future studies examining the results of CPG implementation may lead to the development of new evidence particularly relevant to clinical practice.

IV. Guideline Work Group

Guideline Work Group*	
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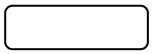
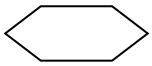
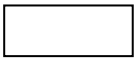
*Additional contributor contact information is available in Appendix F.

V. Algorithm

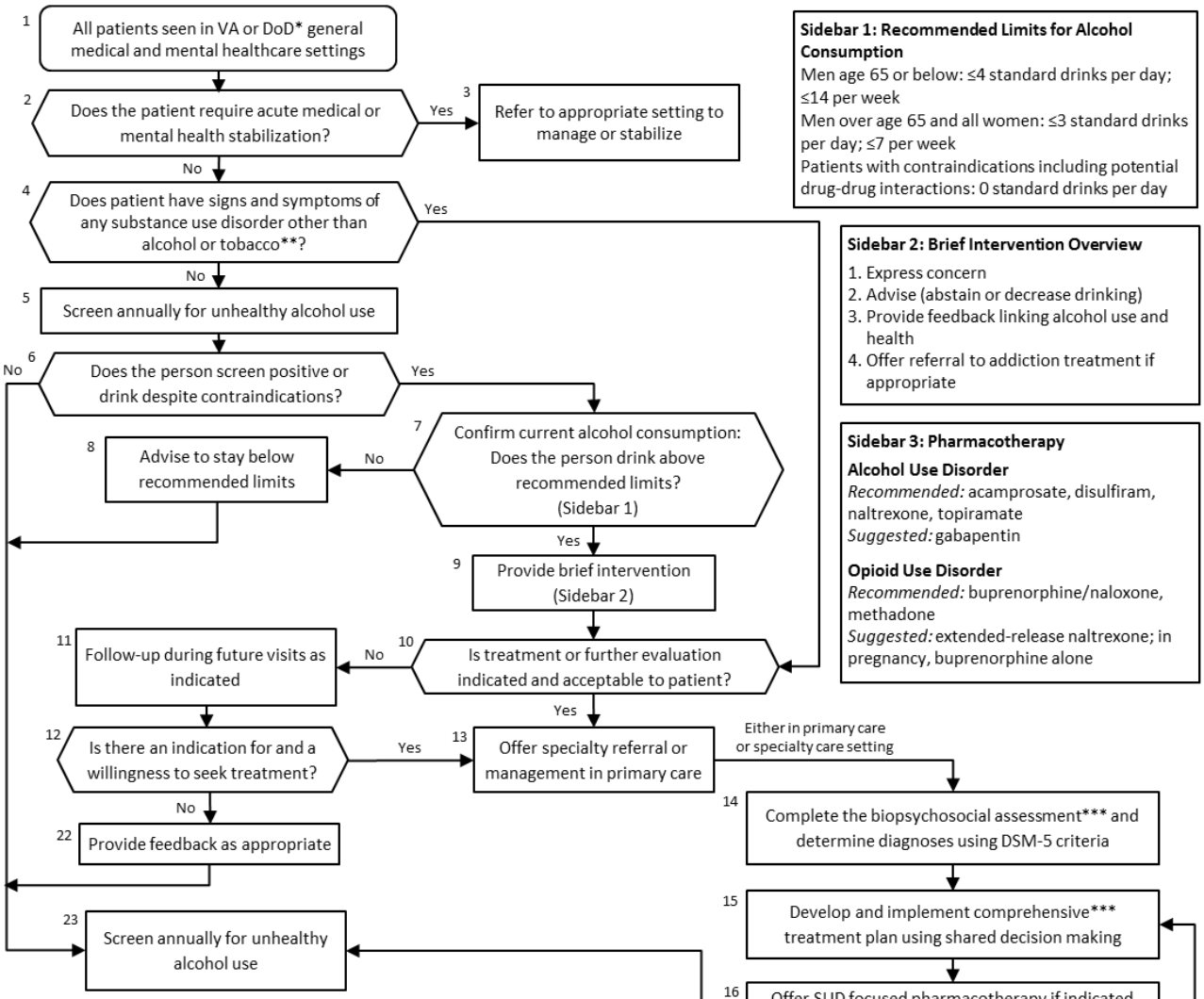
This CPG includes an algorithm which is designed to facilitate understanding of the clinical pathway and decision making process used in management of SUD. The use of the algorithm format as a way to represent patient management was chosen based on the understanding that such a format may promote more efficient diagnostic and therapeutic decision making and has the potential to change patterns of resource use. Recognizing that some clinical care processes are non-linear, the algorithm format allows the provider to follow a simplified linear approach in assessing the critical information needed at the major decision points in the clinical process, and includes:

- An ordered sequence of steps of care
- Recommended observations and examinations
- Decisions to be considered
- Actions to be taken

A clinical algorithm diagrams a guideline into a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm, and arrows connect the numbered boxes indicating the order in which the steps should be followed.[64]

	Rounded rectangles represent a clinical state or condition.
	Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No.
	Rectangles represent an action in the process of care.

A. Module A: Screening and Treatment



Sidebar 1: Recommended Limits for Alcohol Consumption

Men age 65 or below: ≤4 standard drinks per day; ≤14 per week

Men over age 65 and all women: ≤3 standard drinks per day; ≤7 per week

Patients with contraindications including potential drug-drug interactions: 0 standard drinks per day

Sidebar 2: Brief Intervention Overview

1. Express concern
2. Advise (abstain or decrease drinking)
3. Provide feedback linking alcohol use and health
4. Offer referral to addiction treatment if appropriate

Sidebar 3: Pharmacotherapy

Alcohol Use Disorder

Recommended: acamprosate, disulfiram, naltrexone, topiramate

Suggested: gabapentin

Opioid Use Disorder

Recommended: buprenorphine/naloxone, methadone

Suggested: extended-release naltrexone; in pregnancy, buprenorphine alone

Sidebar 4: Components of Addiction-focused Medical Management

- Monitoring adherence, response to treatment, and adverse effects
- Education about AUD/OUD, health consequences, and treatments
- Encouragement to abstain from illicit opioids and other addictive substances
- Encouragement to attend and referral to community supports for recovery
- Encouragement to make lifestyle changes that support recovery

Sidebar 5: SUD and Co-occurring Conditions

- Refer to corresponding section of CPG on SUD and co-occurring conditions
- Consult other VA/DoD CPGs (e.g., Tobacco Use Disorder, Major Depressive Disorder, Posttraumatic Stress Disorder, Low Back Pain, Assessment and Management of Patients at Risk for Suicide, Chronic Multisymptom Illness, Concussion, Diabetes, Hypertension, Chronic Kidney Disease)

Abbreviations

AUD: alcohol use disorder; AUDIT-C: Alcohol Use Disorders Identification Test – Consumption; CPG: clinical practice guideline; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; DoD: Department of Defense; OUD: opioid use disorder; SUD: substance use disorders; VA: Department of Veterans Affairs

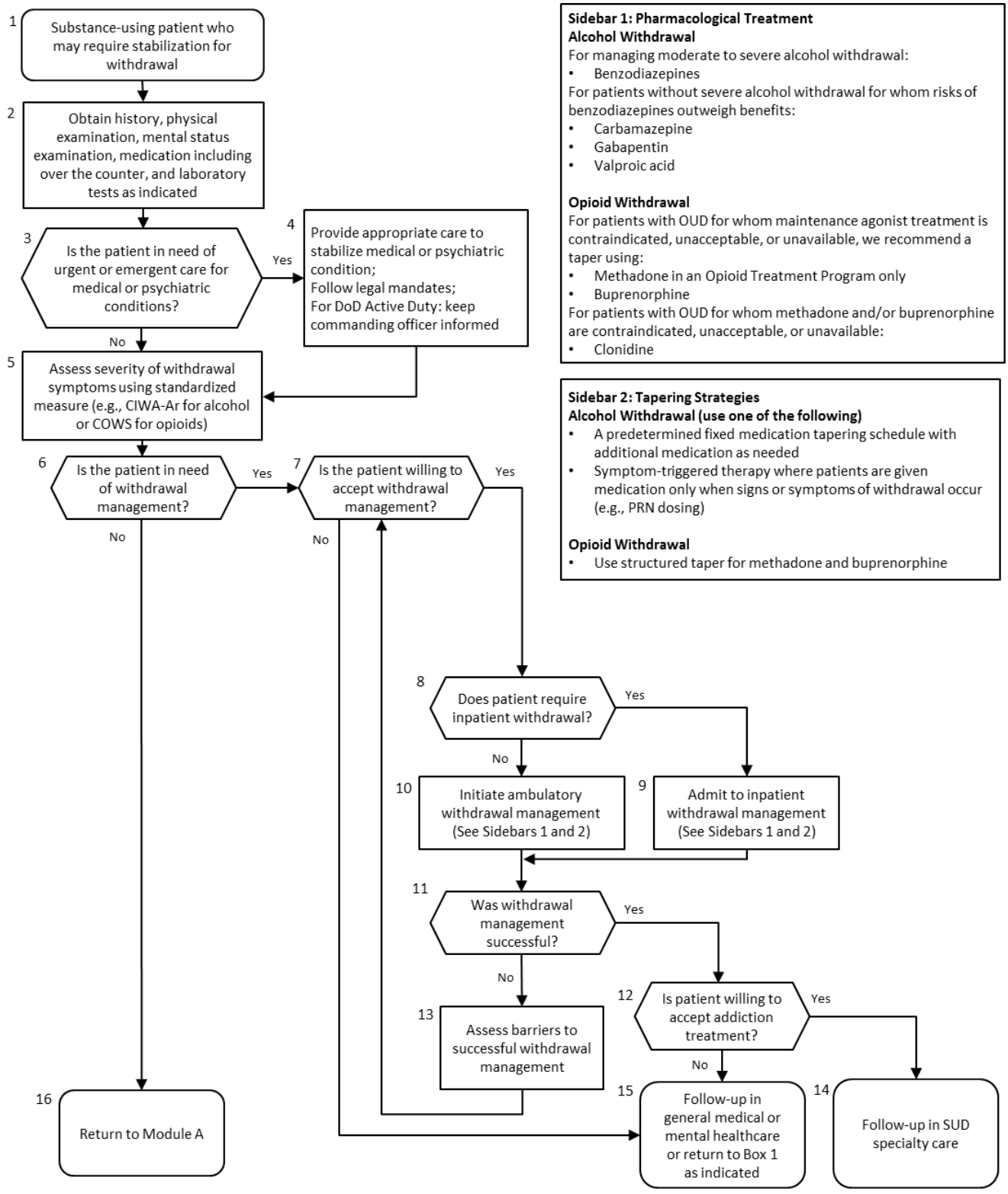
Symbols

*DoD Active Duty: Referral to Specialty SUD Care is required in any incident in which substance use is suspected to be a contributing factor. For refusal, contact Command to discuss administrative and clinical options.

**For patients with tobacco use disorder, refer to VA/DoD CPG on Tobacco Use.

***Specific to specialty care setting

B. Module B: Stabilization



Abbreviations
AUD: alcohol use disorder; CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol-Revised; COWS: Clinical Opiate Withdrawal Scale; DoD: Department of Defense; OUD: opioid use disorder; PRN: as needed

VI. Recommendations

#	Recommendation	Strength*	Category†
A. Screening			
1.	For patients in general medical and mental healthcare settings, we recommend screening for unhealthy alcohol use annually using the three-item Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) or Single Item Alcohol Screening Questionnaire (SASQ).	Strong For	Not reviewed, Amended
B. Brief Alcohol Intervention			
2.	For patients without documented alcohol use disorder who screen positive for unhealthy alcohol use, we recommend providing a single initial brief intervention regarding alcohol-related risks and advice to abstain or drink within nationally established age and gender-specific limits for daily and weekly consumption.	Strong For	Reviewed, New-replaced
C. Determination of Treatment Setting			
3.	For patients with a diagnosis of a substance use disorder, we suggest offering referral for specialty substance use disorder care based on willingness to engage in specialty treatment.	Weak For	Not reviewed, Amended
4.	For patients with substance use disorders, there is insufficient evidence to recommend for or against using a standardized assessment that would determine initial intensity and setting of substance use disorder care rather than the clinical judgment of trained providers.	N/A	Reviewed, New-replaced
D. Treatment			
a. Alcohol Use Disorder			
i. Pharmacotherapy			
5.	For patients with moderate-severe alcohol use disorder, we recommend offering one of the following medications: ▪ Acamprosate ▪ Disulfiram ▪ Naltrexone- oral or extended release ▪ Topiramate	Strong For	Reviewed, New-replaced
6.	For patients with moderate-severe alcohol use disorder for whom first-line pharmacotherapy is contraindicated or ineffective, we suggest offering gabapentin.	Weak For	Reviewed, New-replaced
ii. Psychosocial Interventions			
7.	For patients with alcohol use disorder we recommend offering one or more of the following interventions considering patient preference and provider training/competence: ▪ Behavioral Couples Therapy for alcohol use disorder ▪ Cognitive Behavioral Therapy for substance use disorders ▪ Community Reinforcement Approach ▪ Motivational Enhancement Therapy ▪ 12-Step Facilitation	Strong For	Reviewed, New-replaced

#	Recommendation	Strength*	Category†
b. Opioid Use Disorder			
i. Pharmacotherapy			
8.	For patients with opioid use disorder, we recommend offering one of the following medications considering patient preferences: ▪ Buprenorphine/naloxone ▪ Methadone in an Opioid Treatment Program	Strong For	Reviewed, New-replaced
9.	In pregnant women with opioid use disorder for whom buprenorphine is selected, we suggest offering buprenorphine alone (i.e., without naloxone) considering patient preferences.	Weak For	Reviewed, New-added
10.	For patients with opioid use disorder for whom buprenorphine is indicated, we recommend individualizing choice of appropriate treatment setting (i.e., Opioid Treatment Program or office-based) considering patient preferences.	Strong For	Reviewed, New-replaced
11.	For patients with opioid use disorder for whom opioid agonist treatment is contraindicated, unacceptable, unavailable, or discontinued and who have established abstinence for a sufficient period of time (see narrative), we recommend offering: ▪ Extended-release injectable naltrexone	Strong For	Reviewed, New-replaced
12.	There is insufficient evidence to recommend for or against oral naltrexone for treatment of opioid use disorder.	N/A	Reviewed, New-replaced
13.	At initiation of office-based buprenorphine, we recommend addiction-focused Medical Management (see narrative) alone or in conjunction with another psychosocial intervention.	Strong For	Reviewed, New-replaced
ii. Psychosocial Interventions With or Without Pharmacotherapy			
14.	For patients in office-based buprenorphine treatment, there is insufficient evidence to recommend for or against any specific psychosocial interventions in addition to addiction-focused Medical Management. Choice of psychosocial intervention should be made considering patient preferences and provider training/competence.	N/A	Reviewed, New-replaced
15.	In Opioid Treatment Program settings, we suggest offering individual counseling and/or Contingency Management, considering patient preferences and provider training/competence.	Weak For	Reviewed, New-replaced
16.	For patients with opioid use disorder for whom opioid use disorder pharmacotherapy is contraindicated, unacceptable or unavailable, there is insufficient evidence to recommend for or against any specific psychosocial interventions.	N/A	Reviewed, New-replaced
c. Cannabis Use Disorder			
i. Pharmacotherapy			
17.	There is insufficient evidence to recommend for or against the use of pharmacotherapy in the treatment of cannabis use disorder.	N/A	Reviewed, New-added
ii. Psychosocial Interventions			
18.	For patients with cannabis use disorder, we recommend offering one of the following interventions as initial treatment considering patient preference and provider training/competence: ▪ Cognitive Behavioral Therapy ▪ Motivational Enhancement Therapy ▪ Combined Cognitive Behavioral Therapy/Motivational Enhancement Therapy	Strong For	Reviewed, New-replaced

#	Recommendation	Strength*	Category†
d. Stimulant Use Disorder			
i. Pharmacotherapy			
19.	There is insufficient evidence to recommend for or against the use of any pharmacotherapy for the treatment of cocaine use disorder or methamphetamine use disorder.	N/A	Reviewed, New-added
ii. Psychosocial Interventions			
20.	For patients with stimulant use disorder, we recommend offering one or more of the following interventions as initial treatment considering patient preference and provider training/competence: ▪ Cognitive Behavioral Therapy ▪ Recovery-focused behavioral therapy ◆ General Drug Counseling ◆ Community Reinforcement Approach ▪ Contingency Management in combination with one of the above	Strong For	Reviewed, New-replaced
E. Promoting Group Mutual Help Involvement			
21.	For patients with substance use disorders in early recovery or following relapse, we recommend promoting active involvement in group mutual help programs using one of the following systematic approaches considering patient preference and provider training/competence: ▪ Peer linkage ▪ Network support ▪ 12-Step Facilitation	Strong For	Reviewed, New-replaced
F. Co-occurring Mental Health Conditions and Psychosocial Problems			
22.	Among patients in early recovery from substance use disorders or following relapse, we suggest prioritizing other needs through shared decision making (e.g., related to other mental health conditions, housing, supportive recovery environment, employment, or related recovery-relevant factors) among identified biopsychosocial problems and arranging services to address them.	Weak For	Not reviewed, Amended
G. Follow-up			
23.	We suggest assessing response to treatment periodically and systematically, using standardized and valid instrument(s) whenever possible. Indicators of treatment response include ongoing substance use, craving, side effects of medication, emerging symptoms, etc.	Weak For	Reviewed, New-replaced
24.	For patients who have initiated an intensive phase of outpatient or residential treatment, we recommend offering and encouraging ongoing systematic relapse prevention efforts or recovery support individualized on the basis of treatment response.	Strong For	Not reviewed, Amended
25.	For patients in substance use disorders specialty care, we recommend against automatic discharge from care for patients who do not respond to treatment or who relapse.	Strong Against	Not reviewed, Amended
H. Stabilization and Withdrawal			
a. Assessment			
26.	For patients with alcohol or opioid use disorder in early abstinence, we suggest using standardized measures to assess the severity of withdrawal symptoms such as Clinical Institute Withdrawal Assessment for Alcohol (revised version) (CIWA-Ar) for alcohol or Clinical Opiate Withdrawal Scale (COWS) for opioids.	Weak For	Not reviewed, Amended

#	Recommendation	Strength*	Category†
27.	We recommend inpatient medically supervised alcohol withdrawal management for patients with any of the following conditions: ▪ History of delirium tremens or withdrawal seizures ▪ Inability to tolerate oral medication ▪ Co-occurring medical conditions that would pose serious risk for ambulatory withdrawal management (e.g., severe coronary artery disease, congestive heart failure, liver cirrhosis) ▪ Severe alcohol withdrawal (i.e., Clinical Institute Withdrawal Assessment for Alcohol [revised version] [CIWA-Ar] score ≥20) ▪ Risk of withdrawal from other substances in addition to alcohol (e.g., sedative hypnotics)	Strong For	Reviewed, Amended
28.	We suggest inpatient medically supervised withdrawal for patients with symptoms of at least moderate alcohol withdrawal (i.e., Clinical Institute Withdrawal Assessment for Alcohol [revised version] [CIWA-Ar] score ≥10) and any of the following conditions: ▪ Recurrent unsuccessful attempts at ambulatory withdrawal management ▪ Reasonable likelihood that the patient will not complete ambulatory withdrawal management (e.g., due to homelessness) ▪ Active psychosis or severe cognitive impairment ▪ Medical conditions that could make ambulatory withdrawal management problematic (e.g., pregnancy, nephrotic syndrome, cardiovascular disease, lack of medical support system)	Weak For	Reviewed, Amended
b. Alcohol Use Disorder Stabilization and Withdrawal			
29.	We recommend using one of the following pharmacotherapy strategies for managing alcohol withdrawal symptoms: ▪ A predetermined fixed medication tapering schedule with additional medication as needed ▪ Symptom-triggered therapy where patients are given medication only when signs or symptoms of withdrawal occur (e.g., as needed dosing)	Strong For	Not reviewed, Amended
30.	For treatment of moderate to severe alcohol withdrawal, we recommend using benzodiazepines with adequate monitoring because of documented efficacy and high margin of safety.	Strong For	Reviewed, Amended
31.	For managing mild to moderate alcohol withdrawal in patients for whom risks of benzodiazepines outweigh benefits (e.g., inadequate monitoring available, abuse liability, or allergy/adverse reactions), we suggest considering carbamazepine, gabapentin, or valproic acid as an alternative.	Weak For	Reviewed, New-replaced
32.	We recommend against using alcohol as an agent for medically supervised withdrawal.	Strong Against	Not reviewed, Amended
c. Opioid Use Disorder Stabilization and Withdrawal			
33.	For patients not yet stabilized from opioid use disorder, we recommend against withdrawal management alone due to high risk of relapse and overdose (see Recommendations 8 and 11).	Strong Against	Reviewed, New-replaced

#	Recommendation	Strength*	Category†
34.	Among patients with opioid use disorder for whom maintenance agonist treatment is contraindicated, unacceptable, or unavailable, we recommend using a methadone (in Opioid Treatment Program only) or buprenorphine taper for opioid withdrawal management (see Recommendation 11).	Strong For	Reviewed, New-replaced
35.	For patients with opioid use disorder for whom methadone and buprenorphine are contraindicated, unacceptable, or unavailable, we recommend offering clonidine as a second-line agent for opioid withdrawal management (see Recommendation 11).	Strong For	Reviewed, New-replaced
d. Sedative Hypnotic Use Disorder Stabilization and Withdrawal			
36.	For patients in need of withdrawal management for sedative hypnotics, we suggest one of the following: ▪ Gradually taper the original benzodiazepine ▪ Substitute a longer acting benzodiazepine then taper gradually ▪ Substitute phenobarbital for the addicting agent and taper gradually	Weak For	Not reviewed, Amended

*For additional information, please refer to Grading Recommendations.

†For additional information, please refer to Recommendation Categorization and Appendix E.

A. Screening

Recommendation

1. For patients in general medical and mental healthcare settings, we recommend screening for unhealthy alcohol use annually using the three-item Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) or Single Item Alcohol Screening Questionnaire (SASQ).
   (Strong For | Not reviewed, Amended)

Discussion

Annual Screening for Unhealthy Alcohol Use

Annual screening for unhealthy alcohol use is recommended for all patients based on moderate to high confidence in evidence that alcohol screening followed by brief alcohol counseling is efficacious for reducing drinking.[65,66] Screening should identify patients along the entire continuum of unhealthy alcohol use including those who drink above recommended limits (often called risky or hazardous drinking) and those with severe AUD. Most screen-positive patients will *not* have AUD and will be appropriate candidates for brief alcohol counseling as the initial treatment approach for unhealthy alcohol use.[66] One of two validated brief screens is recommended to identify past-year unhealthy alcohol use: the AUDIT-C [67-70] or a single item alcohol screen for drinking above recommended daily limits (SASQ).[71] More information on the AUDIT-C and SASQ can be found in Table 1.

Selection of an Approach to Unhealthy Alcohol Use Screening in a Particular Setting Should Reflect Local Factors

The AUDIT-C may be preferable in the following situations:

- When the clinician preference is to obtain information regarding:
  - Any drinking (for those with contraindications)
  - Typical drinking (for medication interactions)

- Episodic heavy drinking
- The severity of unhealthy alcohol use provided by the AUDIT-C [72-74]

- When there is a specific service requirement (i.e., VA or DoD quality indicators)
- When an electronic medical record can score the AUDIT-C and provide decision support to the provider

The SASQ screen is easier to integrate into clinician interviews, as primary care clinicians are unlikely to recall response options and scoring for the AUDIT-C.

Table 1. Screening Tools for Unhealthy Alcohol Use

	Alcohol Use Disorders Identification Test- Consumption (AUDIT-C)		Single-Item Alcohol Screening Questionnaire (SASQ)
Items	1. How often did you have a drink containing alcohol in the past year?		1. Do you sometimes drink beer, wine, or other alcoholic beverages? *(Followed by the screening question)* 2. How many times in the past year have you had… Men: 5 or more drinks in a day Women: 4 or more drinks in a day
	Never	0 point	
	Monthly or less	1 point	
	2-4 times per month	2 points	
	2-3 times per week	3 points	
	4 or more times per week	4 points	
	2. On days in the past year when you drank alcohol how many drinks did you typically drink?		
	0, 1, or 2	0 point	
	3 or 4	1 point	
	5 or 6	2 points	
	7-9	3 points	
	10 or more	4 points	
	3. How often did you have 6 or more drinks on an occasion in the past year?		
	Never	0 point	
	Less than monthly	1 point	
	Monthly	2 points	
	Weekly	3 points	
	Daily or almost daily	4 points	
Scoring	The minimum score (for non-drinkers) is 0 and the maximum possible score is 12. Consider a screen positive for unhealthy alcohol use if AUDIT-C score is ≥4 points for men or ≥3 points for women. Note: For VA, documentation of brief alcohol counseling is required for those with AUDIT-C ≥5 points, for both men and women. This higher score for follow-up was selected to minimize the false-positive rate and to target implementation efforts. Follow-up of lower screening scores <5 is left to provider discretion.		A positive screen is any report of drinking 5 or more (men) or 4 or more (women) drinks on an occasion in the past year.

Although qualitative work reflects some reservations among providers about screening for unhealthy alcohol use,[75] evidence does not support provider concerns that delivering brief intervention (BI) based on alcohol screening results adversely affects patients' perceptions of care.[76,77]

More research is needed on the optimal frequency of screening for unhealthy alcohol use [78,79] and alternative methods to promote more efficient and accurate collection of screening data directly from patients.[80,81]

B. Brief Alcohol Intervention

Recommendation

2. For patients without documented alcohol use disorder who screen positive for unhealthy alcohol use, we recommend providing a single initial brief intervention regarding alcohol-related risks and advice to abstain or drink within nationally established age and gender-specific limits for daily and weekly consumption.
   (Strong For | Reviewed, New-replaced)

Discussion

For adults who screened positive for unhealthy alcohol use (e.g., AUDIT-C score ≥3 for women, ≥4 for men), a single brief intervention (BI) is recommended based on several SRs.[65,66,82] These reviews present moderate strength of evidence for efficacy of a BI in reducing consumption outcomes and improving certain health outcomes and moderate confidence that benefits outweigh harms among those with unhealthy alcohol use who do not meet diagnostic criteria for AUD. At the provider's discretion, individuals who are higher risk for AUD (e.g., AUDIT-C score ≥8 or current alcohol use in the context of previously documented AUD treatment or diagnosis) may be further evaluated for AUD diagnosis or referred for further evaluation and managed in accordance with the algorithm.

The reviewed evidence is insufficient to recommend for or against multi-contact BIs over a single BI due to the lack of direct comparisons within studies.[65] Based on this finding, and to minimize opportunity costs resulting from multiple sessions of BI delaying or diverting medical resources that might have been used to address other, more pressing concerns, this guideline recommends a single initial BI. Follow-up BIs may be offered as clinically indicated, based on additional independent risk factors and co-occurring conditions.

Similarly, there is no evidence to suggest that there is a difference in efficacy between 5, 10, or 20 minute interventions [82,83] or that certain components of BIs are more effective than others.[65,84] Two BI elements that are offered consistently in positive randomized clinical trials (RTCs) are: (1) providing individualized feedback on patient's level of alcohol-related risk (i.e., mild, moderate, high) and any alcohol-related adverse health effects; and (2) brief advice to abstain or drink within recommended limits.[65] Additional topics that can be discussed are the benefits of cutting down and effective strategies for reducing alcohol consumption. Motivational interventions focused on supporting the patient in choosing a drinking goal, when he/she is ready to make a change, have been shown to be effective as well[85-90] and can be offered by providers trained in this approach.

The efficacy of a BI is specific to the following consumption outcomes: decrease in mean drinks per week, decrease in number of heavy drinking episodes, and increase in the percentage of patients whose alcohol

consumption is within recommended drinking limits.[65] Similar decreases in alcohol consumption outcomes were shown in women-only trials,[82] in pregnant women,[91,92] and in Veterans,[84] but with a lower quality of evidence. The health outcomes improved with BIs were all-cause mortality,[65] hospitalization rates,[65] and systolic blood pressure.[93]

BIs were found to be effective for adults with unhealthy alcohol use who do not have AUD in a variety of clinical settings, such as primary care,[65,94] emergency department,[95,96] and hospital settings.[97,98] Evidence also shows that BIs are effective when provided by primary care providers,[65] nurses,[65,99] psychologists,[88] or health educators.[100,101] Therefore, we recommend that various providers can administer BIs consistent with this recommendation, as long as it is within the scope of practice and privileges at their facility.

Additional research is needed on the effectiveness of procedures to screen for and address risks related to use of substances other than alcohol and tobacco. According to the USPSTF, the evidence is insufficient to assess the balance of benefits and harms of screening for illicit drug use.[102] Several recent trials have failed to support effectiveness of BIs in primary care for drug problems,[103,104] but one trial found encouraging results of a multi-component intervention.[105]

C. Determination of Treatment Setting

Recommendation

3. For patients with a diagnosis of a substance use disorder, we suggest offering referral for specialty substance use disorder care based on willingness to engage in specialty treatment.
   (Weak For | Not reviewed, Amended)

Discussion

Most patients with alcohol and other SUD do not receive adequate treatment,[21] and many patients will not accept referrals to a specialty clinic for SUD [21,44,106,107] for reasons including, but not limited to, lack of perceived need, fear of stigma, lack of readiness for treatment, lack of resources, time restrictions, etc. While there is evidence that selected patients with SUD can be treated in primary care or general mental healthcare, there is value in initially offering a referral to an SUD specialty clinic when available. A referral to specialty care may help the patient recognize that there is significant concern, which might motivate the patient to address the issue(s) more fully. If a patient has stated that he/she does not want and will not accept a referral to the specialty clinic, then efforts should be made to engage the patient in primary care to include monitoring and treating substance-related problems.

Thus, a referral to specialty SUD care should be offered if the patient has at least one of the following:

- May benefit from additional evaluation of his/her substance use and related problems
- Has been diagnosed as having an SUD
- Is willing to engage in specialty care

Benefits of offering a referral far outweigh any associated harms, and patients vary widely in their values and preferences regarding engaging in specialty care. The offer of a referral expresses care and concern on the part of the provider and allows an opportunity for patients to receive sufficient information for

reasoned decision making. Referrals may have implications for resource utilization in both the primary and specialty care settings and may not be able to be based on positive screening results alone.

Recommendation

4. For patients with substance use disorders, there is insufficient evidence to recommend for or against using a standardized assessment that would determine initial intensity and setting of substance use disorder care rather than the clinical judgment of trained providers.
   (N/A | Reviewed, New-replaced)

Discussion

Identifying the appropriate level of care in SUD treatment is a challenge, and numerous variables, including patient preference, patient motivation, patient willingness, and available resources can be taken into consideration. However, there is a lack of clear evidence that any specific factor accurately predicts the optimal level or intensity of care. The American Society of Addiction Medicine Patient Placement Criteria (The ASAM Criteria, 2013) [108] have been widely promulgated as a system to determine level of care based on assessment of six dimensions (acute intoxication and/or withdrawal potential; biomedical conditions and complications; emotional, behavioral or cognitive conditions and complications; readiness to change; relapse, continued use, or continued problem potential; and recovery/living environment), but controlled trials evaluating placement outcomes based on standardized assessment of these dimensions are lacking. Future research is needed to evaluate whether recently developed software to conduct the multidimensional assessment and yield an algorithmically derived placement recommendation leads to better outcomes than clinical judgment that may rely more generally on the six ASAM assessment dimensions and placement principles.

D. Treatment

a. Alcohol Use Disorder

i. Pharmacotherapy

Recommendations

5. For patients with moderate-severe alcohol use disorder, we recommend offering one of the following medications:
   - Acamprosate
   - Disulfiram
   - Naltrexone- oral or extended release
   - Topiramate

   (Strong For | Reviewed, New-replaced)

6. For patients with moderate-severe alcohol use disorder for whom first-line pharmacotherapy is contraindicated or ineffective, we suggest offering gabapentin.
   (Weak For | Reviewed, New-replaced)

Discussion

Naltrexone, acamprosate, disulfiram, and topiramate are recommended for the treatment of AUD based on RCTs [109] and several SRs/meta-analyses.[110-112] The clinical trials reviewed were based on DSM-IV

criteria for alcohol dependence which is equivalent to DSM-5 criteria for moderate-severe AUD. These medications should be offered in conjunction with a psychosocial intervention and considering the preferences of appropriately informed patients. Dosing of these pharmacotherapies should be consistent with medication trials and published recommendations.

In the absence of contraindications, there is insufficient evidence to recommend for or against the routine use of one of these recommended medications over another; therefore, treatment should be individualized considering patient preferences. These medications are presented below in alphabetical order. Additional information can be found in Appendix B, Table B-1. This information includes indications, contraindications, warnings/precautions, baseline evaluation, dosage and administration, alternative dosing schedules, dosing in special populations, adverse effects, drug interactions, monitoring, and patient education.

Acamprosate

Acamprosate may act by normalizing central glutamatergic dysregulation in AUD, thereby relieving symptoms of prolonged alcohol withdrawal.[113] Numerous European trials found acamprosate effective in reducing drinking days, increasing complete abstinence, and lengthening time to relapse; however, U.S. trials failed to show benefit.[112] These discordant results may have been due to methodological differences between the U.S. and European studies including: site of pretreatment detoxification, duration of pretreatment abstinence, duration of study treatment, concomitant medications, nature and intensity of accompanying psychosocial treatment, outcome measures used, and severity of participants' AUD.[113] The three doses per day and large tablet size present a challenge to many patients and can negatively affect treatment adherence. Acamprosate should be considered in patients with AUD who are also taking prescribed opioids or who have significant hepatic damage/impairment, as it is the only first-line drug recommended by the SUD CPG Work Group that is not subject to hepatic clearance. Patients who are well-suited for acamprosate include those who are highly motivated, abstinent prior to initiation, and not discouraged by the three times per day dosing burden. Some patients and providers may opt for other agents dosed once daily depending upon patient preferences and values.

Disulfiram

Patients taking disulfiram should avoid ingestion of alcohol due to the expectation of a toxic reaction if alcohol is consumed; thus, it has been suggested that the optimal assessment of disulfiram efficacy has resulted from open-label trials where patient awareness of active treatment allowed treatment to have its full preventive effect.[111] Disulfiram supports a behavioral treatment paradigm in which alcohol consumption is consistently and quickly followed by adverse effects in the form of the alcohol-disulfiram reaction. The human tendency to avoid punishment may affect not only alcohol consumption but also adherence to disulfiram, thus reducing its effectiveness when administration is unsupervised. A meta-analysis of 22 RCTs of disulfiram, showed no advantage to disulfiram compared to control conditions in blinded trials, modest advantage in open-label unsupervised trials, and a moderately large effect size in supervised versus unsupervised open-label trials.[111] Because the action of disulfiram depends on the expectation of adverse effects, the drug should not be given to patients who are unable to consider the consequences of alcohol consumption while taking disulfiram. Disulfiram is thus best suited to patients who have made an informed choice of this type of treatment, are highly compliant, and are under close medical supervision. Because of the risk of significant toxicity, the risks and benefits of disulfiram should be

carefully considered. Disulfiram should only be used when abstinence is the goal and when initiated with addiction-focused counseling. Verification of abstinence and the informed consent discussion with the patient should be documented.

Naltrexone

Naltrexone is an opioid antagonist available for once-daily oral administration and in an extended-release suspension for once-monthly intramuscular injection. The two formulations have not been directly compared to evaluate whether the long-acting injectable formulation improves treatment adherence and clinical outcomes;[112] however, injectable naltrexone should be considered when medication adherence is a significant concern, and the patient is accepting of treatment that requires monthly injections by a provider. Naltrexone injection must be stored under refrigeration, and provision to Service Members deployed to remote locations may be problematic. In a multicenter trial (Combining Medications and Behavioral Interventions [COMBINE]) comparing oral naltrexone and/or acamprosate to double placebo with addiction-focused Medical Management (see Addiction-focused Medical Management for additional information) and/or Combined Behavioral Intervention (CBI), patients receiving addiction-focused Medical Management with naltrexone, CBI, or both, fared better on drinking outcomes than those receiving acamprosate or double placebo.[114]

Topiramate

Topiramate is believed to decrease alcohol reinforcement and the propensity to drink by reducing craving for alcohol through antagonism of glutamate receptors and inhibition of dopamine release.[110] Topiramate is not Food and Drug Administration (FDA) approved for AUD but is recommended here because there is moderate quality evidence which favors significant reduction in heavy drinking and promotion of abstinence with its use [110,112,115] as well as one recent pilot trial showing benefit with Veterans who had AUD and co-occurring PTSD.[109] These benefits may be accompanied by well-documented side effects which include paresthesia/numbness, anorexia, taste abnormalities, cognitive impairment, and rash. Fortunately, some common side effects can usually be managed by lowering the topiramate dose. A lower dose of 200 mg daily has been shown to be effective [110] and is less prone to causing side effects than higher doses; thus, the 200 mg daily dose is the recommended regimen.

Gabapentin

Gabapentin is suggested as an option for patients with AUD for whom first-line pharmacotherapy is contraindicated or ineffective. The effects of gabapentin likely occur through modulation of γ-aminobutyric acid (GABA) activity in the amygdala associated with AUD. One RCT in 150 patients indicated gabapentin significantly improved the rates of abstinence and heavy drinking; however, the single-site setting and high dropout rate in this study raise concerns regarding its generalizability and potential for bias.[116] Another trial indicated that the addition of gabapentin to oral naltrexone improved drinking outcomes over those obtained with naltrexone alone.[112] The need for more than once-daily dosing may make treatment adherence difficult for some patients. Also, there are increasing concerns regarding the abuse potential of gabapentin if taken at doses far exceeding therapeutic recommendations.[117] However, when taken as directed, gabapentin has a high margin of safety, and many primary care providers have experience prescribing the drug for non-AUD indications. Gabapentin may be a treatment consideration for patients with co-occurring neuropathic pain or in patients with hepatic disease who cannot take acamprosate.

Other medications, not recommended

Two RCTs of baclofen provided low quality evidence for the drug's efficacy but had inconsistent findings regarding consumption outcomes.[112] Additional studies of better overall quality are needed to make a recommendation for or against the use of baclofen for AUD. Abrupt withdrawal of baclofen can be associated with hallucinations and seizures.

There are no large, randomized, double-blind studies of valproic acid; however, two very small trials provided low to moderate quality evidence for a positive effect on alcohol consumption.[112]

The use of buspirone, citalopram, fluoxetine, and quetiapine in patients with AUD showed either no benefit or an inconsistent benefit in studies typically providing a very low or low overall quality of evidence.[112,118]

ii. Psychosocial Interventions

Recommendation

7. For patients with alcohol use disorder we recommend offering one or more of the following interventions considering patient preference and provider training/competence:
    - Behavioral Couples Therapy for alcohol use disorder
    - Cognitive Behavioral Therapy for substance use disorders
    - Community Reinforcement Approach
    - Motivational Enhancement Therapy
    - 12-Step Facilitation

    (Strong For | Reviewed, New-replaced)

Discussion

A brief description of these psychosocial interventions and evidence for their use for patients with AUD can be found below. Additional information about these interventions, as well as the appropriateness of their use for patients with specific types of SUD, can be found in Appendix C.

Most versions of Behavioral Couples Therapy (BCT) are focused both on reducing alcohol use in the identified patient and on improving overall marital satisfaction for both partners. To improve relationship functioning, BCT uses a series of behavioral assignments to increase positive feelings, shared activities, and constructive communication because improving these relationship factors is also conducive to sobriety.

Cognitive Behavioral Therapy (CBT) for AUD focuses on teaching patients to modify both thinking and behavior related to alcohol use, as well as to change other areas of life functionally related to alcohol use. Patients learn to track their thinking and activities and identify the affective and behavioral consequences of those thoughts and activities, including increases in craving and episodes of alcohol use. Patients then learn techniques to change thinking and behaviors that contribute to alcohol use, and to strengthen coping skills, improve mood and interpersonal functioning, and enhance social support. Treatment incorporates structured practice outside of session, including scheduled activities, self-monitoring, thought recording and challenging, and interpersonal skills practice.

Community Reinforcement Approach (CRA) is a comprehensive cognitive-behavioral intervention for the treatment of AUD that focuses on environmental contingencies that impact and influence the patient's

behavior. Given that environmental contingencies play a crucial role in an individual's addictive behavior and recovery, CRA utilizes familial, social, recreational, and occupational events to support the individual in changing his or her drinking behaviors so that a sober lifestyle is more rewarding than one that is dominated by alcohol. CRA integrates several treatment components, including increasing positive reinforcement, learning new coping behaviors, and involving significant others in the recovery process. In some versions of CRA, incentives are also provided for positive behaviors, such as attending treatment, taking medication, or being abstinent.

Motivational Enhancement Therapy (MET) is a less intensive psychosocial intervention for patients with AUD. MET uses principles of motivational interviewing (MI) to heighten awareness of ambivalence about change, promote commitment to change, and enhance self-efficacy. MET differs from MI in that it is a more structured intervention that is based to a greater degree on systematic assessment with personalized feedback. The therapeutic style uses MI to elicit patient reactions to assessment feedback, commitment to change, and collaboration on development of an individualized change plan. Involvement of a significant other is encouraged in at least one of the MET sessions.

12-Step Facilitation (TSF) therapy aims to increase the patient's active involvement in Alcoholics Anonymous (AA) or other 12-step-based group mutual help resources. This approach is systematized in a manual and is delivered as 12 sessions of individual therapy in which the therapist actively encourages engagement in AA and walks the patient through the first four steps of the AA program. The first part of each session includes reviewing relevant events of the last week (including urges to use, drinking behavior, and recovery-oriented activities) and a homework assignment. The middle portion introduces new material related to the 12-steps. The conclusion of the session includes a homework assignment and development of a plan for recovery-oriented activities (meeting attendance, sponsor contact). Other interventions based on TSF have also focused on increasing positive social support outside of 12-step programs.

Three SRs have indicated that CBT is generally more effective than minimal or control comparators for individuals with AUD, but not superior to other active treatments.[119-121] Other individual studies of CBT in patients with AUD and mental health comorbidities generated mixed results, with one study finding positive effects [122] and two finding positive effects at some, but not all, follow-up points.[123,124]

The combination of CBT plus MI appears to be more effective than comparison conditions for individuals with AUD and co-occurring anxiety or depression disorders.[125] Studies have consistently found that BCT and CRA produce improved alcohol use outcomes during treatment and/or follow-up, relative to various active comparison conditions.[126-129] BCT generally has positive effects on measures of marital satisfaction as well.

As a stand-alone treatment, MET provided over 3-4 sessions yielded comparable benefits to more intensive manualized interventions (CBT or TSF) involving 8-12 sessions.[130,131] TSF and other treatments designed to increase participation in self/mutual help programs and other sources of social support in the community (See Promoting Group Mutual Help Involvement for additional information) have consistently increased participation in these programs and produced greater improvements in some drinking outcomes compared to CBT or MET.[130]

Confidence in the quality of the evidence regarding the effectiveness of these interventions for the treatment of AUD is moderate, with benefits outweighing harms. Because of variations in patient values and preferences for psychosocial intervention approaches, we recommend offering a menu of options using a shared decision making (SDM) approach. The primary concerns regarding the use of these interventions are that they require considerable training to implement with fidelity and are resource-intensive to deliver. The research evidence is based almost entirely on studies in which these interventions were delivered individually to patients, whereas most AUD treatment in the VA and DoD is delivered in groups. Finally, little is known about the effectiveness of some of these interventions within specific subgroups, most notably the effectiveness of BCT in women and lesbian, gay, bisexual, and transgender individuals.

b. Opioid Use Disorder

i. Pharmacotherapy

Recommendation

8. For patients with opioid use disorder, we recommend offering one of the following medications considering patient preferences:
    - Buprenorphine/naloxone
    - Methadone in an Opioid Treatment Program

    (Strong For | Reviewed, New-replaced)

9. In pregnant women with opioid use disorder for whom buprenorphine is selected, we suggest offering buprenorphine alone (i.e., without naloxone) considering patient preferences.
    (Weak For | Reviewed, New-added)

10. For patients with opioid use disorder for whom buprenorphine is indicated, we recommend individualizing choice of appropriate treatment setting (i.e., Opioid Treatment Program or office-based) considering patient preferences.
    (Strong For | Reviewed, New-replaced)

11. For patients with opioid use disorder for whom opioid agonist treatment is contraindicated, unacceptable, unavailable, or discontinued and who have established abstinence for a sufficient period of time (see narrative), we recommend offering:
    - Extended-release injectable naltrexone

    (Strong For | Reviewed, New-replaced)

12. There is insufficient evidence to recommend for or against oral naltrexone for treatment of opioid use disorder.
    (N/A | Reviewed, New-replaced)

13. At initiation of office-based buprenorphine, we recommend addiction-focused Medical Management (see narrative) alone or in conjunction with another psychosocial intervention.
    (Strong For | Reviewed, New-replaced)

Discussion

Medications in General—Opioid Agonists and Antagonists

Buprenorphine and methadone are recommended for the treatment of opioid use disorder (OUD) based on high quality evidence from multiple RCTs and meta-analyses. High quality evidence supports the use of medication-assisted treatment using methadone or buprenorphine over psychosocial treatment alone to improve outcomes for OUD.[132-147] Extended-release injectable naltrexone is also recommended for maintenance treatment of OUD based on moderate quality evidence. In addition to the quality of evidence (listed below under each medication), our recommendations are based on decisions regarding three other domains: the balance of desirable and undesirable medication effects, values and preferences of patients, and other associated implications, such as DoD mission-readiness. If a patient refuses or defers medication-assisted treatment, we suggest using a motivational approach to encourage reconsideration. One motivational strategy is to provide treatment options, as there may be variations in values and preferences among patients with OUD.

Opioid Agonists

Opioid agonist therapy (OAT) for OUD consists of administering a medication, such as methadone or sublingual or buccal buprenorphine, in combination with a comprehensive range of medical, counseling, and rehabilitative services, as indicated. By administering an opioid to prevent withdrawal, to reduce craving, and to reduce the effects of illicit opioids, the patient with OUD is able to focus more readily on recovery activities. In addition, OAT has been associated with a reduction in human immunodeficiency virus (HIV) risk behavior and drug-related criminal behavior. When compared to medically supervised withdrawal attempts, OAT is more successful in achieving the long-term goal of reducing opioid use and the associated negative medical, legal, and social consequences, including death from overdose.

Five SRs showed that using opioid agonists for the treatment of OUD was effective in both licensed Opioid Treatment Programs (OTPs) as well as within general medical settings.[133,135,143,144,148] OTPs are structured, licensed facilities that are not available within the DoD, nor in many VA facilities or communities. Some OTPs provide comprehensive services including individual counseling, group therapy, and family counseling.[149] OTPs can provide opioid maintenance and withdrawal management using methadone or buprenorphine, although most OTPs predominately provide methadone. In the U.S., methadone can be dispensed within OTPs only, whereas buprenorphine can also be prescribed by physicians in office-based settings, including primary care, outpatient specialty SUD treatment, and mental health clinics. Provision of care at OTPs is highly regulated with provider- and patient-level requirements including limitations on the number of take-home medication doses, drug screens required at least eight times annually, and implementation of appropriate psychosocial interventions. For some patients with OUD, OTPs may not be feasible due to their distance from home or the impact on mission-readiness in the DoD.

Overall, the benefits of the recommended treatments outweigh their potential harms. While offering methadone or buprenorphine is recommended, patients' values and preferences for treatments may vary, particularly for Active Duty military and those in safety-sensitive positions. Some patients may want office-based care using buprenorphine, some may want methadone or buprenorphine treatment in OTPs, while others may refuse agonist medication altogether.

Buprenorphine

Buprenorphine treatment includes both the buccal and sublingual forms of the mono-product buprenorphine or combination-product buprenorphine/naloxone. In contrast to the more highly controlled methadone, treatment with buprenorphine can be provided by physicians who have received a waiver from the SAMHSA and have a special Drug Enforcement Administration (DEA) number. To qualify for a waiver under the Drug Addiction Treatment Act of 2000 (DATA 2000), a licensed physician (MD or DO) must complete an approved eight-hour training course or meet other specific criteria.[150] For the first year a physician has her or his waiver, the physician may only dispense or prescribe buprenorphine for up to 30 patients at a time under the provisions of DATA 2000. After the first year the qualified physician can apply to SAMHSA to raise her or his treatment limit to 100 patients. Given active discussion of changes to regulations related to the use of buprenorphine, providers can find updates at http://www.samhsa.gov/medication-assisted-treatment.

RCTs have demonstrated the effectiveness of buprenorphine treatment.[136,137,151] In addition, buprenorphine has been shown to be effective in a variety of real-world settings for different patient populations, including those who are homeless or infected with HIV.[152-157] Meta-analyses of studies comparing buprenorphine treatment to methadone treatment indicate that, overall, both are equivalent in terms of suppressing illicit opioid use, but that methadone has slightly better treatment retention.[134]

We found high quality evidence that buprenorphine is more effective than oral naltrexone or placebo therapy in improving opioid consumption and time to relapse.[136] Moderate evidence also supports higher versus lower dosing of buprenorphine for improving treatment retention.[133] Low quality evidence supports higher versus lower dosing of buprenorphine or methadone for improving opioid consumption outcomes. We found low quality evidence favoring flexible versus fixed buprenorphine dosage regimens.[135] Because of significantly higher attrition in the lower dose and fixed dose groups, the confidence in the final opioid consumption estimates was reduced.

Buprenorphine for Maintenance versus Taper

We found high quality evidence supporting buprenorphine for maintenance (14 weeks) over taper (four weeks) for improving treatment retention and moderate quality evidence supporting buprenorphine for improving opioid consumption outcomes. The high loss to follow-up in the group receiving the four-week taper compromised the confidence in the average rates of opioid use between the two conditions. Other considerations, such as resource use, also favor maintenance because of human capital and financial costs of relapse including opioid overdose death after taper. If taper is chosen, then we recommend extended-release injectable naltrexone upon completion of taper. Moderate quality evidence indicates that a slower taper is better than a faster taper with benefits outweighing risks. There is some variation in preferences, particularly for those in safety-sensitive positions.[158]

Buprenorphine- Use in Pregnancy

Women who have OUD may consider becoming pregnant or may be pregnant. With the rise in prescribed and illicitly used opioids, it was reported in 2012 that the incidence of identification of maternal opioids at delivery increased more than four-fold in the past decade. It was also reported that the incidence of neonatal opioid withdrawal identified at delivery increased almost three-fold in the past decade.[159,160] Since the 1960s, methadone has been the most prominent medication to treat pregnant women with OUD

and has been associated with good maternal and neonatal outcomes.[161,162] Since the advent of buprenorphine to treat OUD in 2002, there has been increased interest in using this medication to treat OUD in pregnancy.

Several studies have shown that buprenorphine can be used successfully in pregnancy.[139,163-165] In a double-blind, double-dummy, flexible-dosing RCT comparing buprenorphine treatment to methadone treatment for pregnant women with OUD, Jones et al. (2010) found that infants born to mothers treated with buprenorphine compared to infants born to mothers treated with methadone required significantly lower amounts of morphine to treat neonatal abstinence syndrome. Neonates born to mothers treated with buprenorphine had shorter hospital stays and significantly shorter duration of treatment for neonatal abstinence syndromes.[166] In terms of pregnancy-related complications, there was no difference between methadone and buprenorphine for maternal adverse events. There was also no difference in maternal serious adverse events between methadone and buprenorphine.[166] If treatment retention is the main priority, women on OAT should likely be on methadone as methadone treatment programs are likely to offer more structure to non-pharmacotherapy and pharmacotherapy treatment than office-based treatment with buprenorphine. If having fewer neonatal complications or serious maternal complications during delivery is a priority, we recommend using buprenorphine. Furthermore, patient choice is an important factor in deciding between methadone and buprenorphine in pregnancy. However, availability of medication should be taken into consideration, as buprenorphine is more widely available in some settings than methadone.

For stabilization in pregnant women, patients could be administered immediate maintenance therapy with no taper. If the patient chooses to taper, then taper should be used the same as in other patients. See Stabilization and Withdrawal for specific recommendations to minimize withdrawal symptoms.

It is important to note that the mono-product of buprenorphine (not buprenorphine/naloxone) was used in the four previously cited clinical trials in order to minimize risks to the fetus. Both buprenorphine and naloxone are FDA-labeled as Pregnancy Category C, that is, “animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.”[167] FDA labeling for Suboxone® (buprenorphine/naloxone) states “SUBOXONE® sublingual tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.” Two small pilot studies have found similar outcomes for pregnant women with OUD and their neonatal offspring who were treated with buprenorphine-naloxone combination product compared to published outcomes for methadone or buprenorphine mono-product [168] or compared to matched controls receiving methadone.[169] Clinicians should weigh the unknown risks of long-term harm to the fetus from limited exposure to naloxone in the combination product versus the risks of misuse or diversion posed by prescribing the mono-product to the mother during pregnancy.

Buprenorphine- Determining Appropriate Setting

First-line treatment for OUD is OAT which can be provided in federally regulated Opioid Treatment Programs (OTPs) or through Office-based Opioid Therapy (OBOT). Buprenorphine and long-acting injectable naltrexone can be provided in a variety of settings, whereas methadone for the treatment of OUD can only be provided in federally regulated OTPs.[170]

OBOT using buprenorphine can be provided in both general healthcare and specialty SUD treatment settings by appropriately credentialed physicians in accordance with DATA 2000.[170] Buprenorphine is the only opioid agonist medication approved for OBOT. For OBOT using buprenorphine history and physical exam are recommended as are capacity to obtain laboratory tests including urine drug testing. Capacity to provide or refer to counseling and treatment services if indicated is required.

Clinical judgment suggests that some patients will respond better in an OTP versus OBOT (Table 2).

Table 2: Patient Characteristics Suggestive of Suitability for OBOT versus OTP

Criteria	OBOT	OTP
Can an office-based setting provide needed resources for the patient?	Yes	No
Patient's psychosocial supports	Good	Poor
Previous failed treatment attempts with opioid maintenance	None/few	Many
Difficulty accessing OTP (geographic distance, DoD mobility requirements, etc.)	Yes	No
Pain condition that requires ongoing or recurrent treatment with short-acting opioids	No	Yes

Abbreviations: DoD: Department of Defense; OBOT: Office-based Opioid Therapy; OTP: Opioid Treatment Programs

Methadone and Methadone Maintenance Therapy

High quality evidence favors methadone over placebo or non-pharmacologic intervention for opioid use and treatment retention.[148] The benefits of methadone maintenance therapy (MMT) outweigh harms for a wide variety of secondary outcome measures as well. Methadone has been shown to reduce the morbidity and criminality associated with heroin use, improve social engagement and vocational productivity, and prevent the spread of blood borne diseases associated with sharing needles.[135]

Despite strong evidence of benefit, both clinicians and patients have varying preferences regarding MMT. Some clinicians, for example, are concerned about methadone's adverse effects including prolonged time from the start of the Q wave to the end of the T wave (QT interval) and respiratory depression. Methadone is less widely available due to the regulatory framework which restricts methadone treatment to OTPs with strict guidelines for dosing, supervised treatment, and associated services. In addition, MMT has mission-readiness implications for Active Duty personnel. Military personnel are not deployed if they are on MMT.

Decades of experience with MMT have yielded additional evidence to enhance treatment outcomes. The optimal dosage of methadone for retention in treatment is ≥60 mg/day. In addition, flexible dosage strategies are better than fixed dosage strategies in improving retention.[135] Under usual practices, a stable target dose is >60 mg/day, and many patients will require considerably higher doses in order to achieve a pharmacologic blockade of reinforcing effects of illicit opioids. Risk of relapse to opioid use from lower doses must be weighed against risks of adverse events such as sedation, constipation, hyperalgesia, prolongation of cardiac conduction, and torsade de pointes. Torsade de pointes is an often fatal, but extremely rare, adverse event. Two recent studies found no correlation between methadone daily dose and QTc (the heart rate corrected time from the start of the Q wave to the end of the T wave).[171,172]

Other risk factors must be considered such as history of heart disease and concurrent medications that also prolong QTc.

Opioid Antagonists

Naltrexone Therapy

Moderate quality evidence supports the use of long-acting injectable naltrexone for OUD.[173] The opioid antagonist naltrexone may be prescribed in either an oral or extended release injectable form. Long-acting injectable naltrexone can also be provided in both general healthcare and specialty SUD treatment settings. An RCT demonstrated that extended-release injectable naltrexone reduced opioid consumption and improved retention in treatment for patients with OUD.[173] While documented abstinence from alcohol is not required for therapeutic benefit with injectable naltrexone, even greater benefit may be seen in patients who achieve some duration of alcohol abstinence (e.g., two to four days) prior to the initial injection of naltrexone.[174]

While oral naltrexone was originally developed for treatment of OUD, a meta-analysis of 13 studies comparing oral naltrexone to placebo, another medication, or non-pharmacologic treatment found no difference between naltrexone and the control conditions in treatment retention or opioid use. A major barrier to treating OUD with oral naltrexone was treatment retention, which averaged 28%.[175] Three additional clinical trials addressed concerns about medication adherence (using a riboflavin marker or observed dosing) but found inconsistent results with regard to treatment retention and opioid consumption outcomes. For treatment retention, one trial favored naltrexone over placebo [176] while another found no difference between naltrexone and treatment as usual (TAU).[177] For opioid consumption, one trial favored naltrexone [176] while two found no difference between oral naltrexone and placebo [136] or TAU.[177] Further research is needed to determine whether additional measures to improve treatment retention (e.g., Contingency Management [CM]) together with measures to improve medication adherence would reduce opioid consumption. Based on the available evidence, oral naltrexone cannot be recommended for treatment of OUD.[175-177] There is insufficient evidence of efficacy of oral naltrexone, and the staff time that is associated with observing and monitoring medication adherence must be taken into consideration when making the decision to use oral naltrexone.

Buprenorphine and Addiction-focused Medical Management

Buprenorphine should be initiated along with a psychosocial intervention ranging from addiction-focused Medical Management (see Addiction-focused Medical Management for additional information) to more intensive psychosocial interventions. Available evidence has examined use of buprenorphine provided with psychosocial interventions. Addiction-focused Medical Management is an important adjunct for buprenorphine treatment in office-based settings.

Several studies have shown that adding more addiction-specific counseling provides no added benefit when compared with addiction-focused Medical Management alone.[51,53,54]

Weiss et al. (2011) conducted a multisite randomized controlled clinical trial of medically and psychiatrically stable patients with prescription OUD, 42% of whom reported concurrent chronic pain.[53] All participants received buprenorphine and addiction-focused Medical Management. After an initial 30-60 minute evaluation and feedback session, addiction-focused Medical Management consisted of 15-20-

minute twice weekly tapering to biweekly individual sessions with the physician, as described in the introductory addiction-focused Medical Management section. The study found no added benefit of additional twice weekly tapering to biweekly 45-60 minute individual counseling sessions with a counselor.

Similarly, Fiellin et al. (2013) examined a sample of patients with OUD receiving buprenorphine in primary care. [54] Patients with concurrent alcohol, benzodiazepine or cocaine use disorder or those who were psychiatrically unstable were referred to specialty SUD care. All patients received a 45-60 minute initial evaluation and feedback session with the prescribing physician and eight 15-20 minute addiction-focused Medical Management sessions over 12 weeks. For these psychiatrically stable patients with OUD, there was no evidence of added benefit for the addition of 12 weekly individual Cognitive Behavioral Therapy (CBT) sessions. A study by Ling et al. (2013) evaluated four different behavioral interventions in combination with pharmacotherapy and addiction-focused Medical Management.[51] Among outpatients selected for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnosis of opioid dependence, lack of co-occurring alcohol or benzodiazepine misuse, and good general mental and physical health, little benefit was obtained when adding behavioral treatment to OBOT and manually-driven addiction-focused Medical Management.

Because OBOT patients who received addiction-focused Medical Management alone received a standard set of psychosocial interventions that may not be routinely provided in many clinics, one must be cautious in overgeneralizing the results described above to all populations and treatment settings. Addiction-focused Medical Management should include drug use monitoring and psychosocial support including motivational interviewing (MI) or a shared decision-making (SDM) approach and encourage participation in mutual help programs, even if no specific, manualized treatment is provided. One suggested approach is to consider addiction-focused Medical Management alone for less complicated patients and to reserve adding ancillary counseling services for those patients who have suboptimal outcomes or who have more complex psychosocial needs.

Research into the minimum components of physician management that provide beneficial outcomes for particular patients is needed. In addition, patients who have OUD with primarily prescription drug use versus heroin drug use, and who seek care in primary care may be different in treatment needs and response to treatment.[178] Thus research is needed to understand how to “match” appropriate treatments to patients who seek OUD treatment in primary care settings.

In both the Weiss et al. (2011) and Fiellin et al. (2006) studies, outcomes reported were addiction-related. It is not known whether other patient or provider outcomes are improved by the addition of CBT or additional OUD counseling beyond addiction-focused Medical Management.[52,53] Further research should examine the non-addiction related benefits of providing additional psychotherapy to patients in primary care settings on buprenorphine or when the physician is not well versed in addiction-focused Medical Management. Patients may also refuse non-medical, ancillary treatments, and it is unclear how best to help such patients.

ii. Psychosocial Interventions

Recommendation

14. For patients in office-based buprenorphine treatment, there is insufficient evidence to recommend for or against any specific psychosocial interventions in addition to addiction-focused Medical Management. Choice of psychosocial intervention should be made considering patient preferences and provider training/competence.
    (N/A | Reviewed, New-replaced)

Discussion

A brief description of these psychosocial interventions and evidence for their use for patients with OUD can be found below. Additional information on these interventions, as well as the appropriateness of their use for patients with specific types of SUD, can be found in Appendix C.

OBOT using buprenorphine has increased availability of OAT to a wider variety of persons with OUDs. According to the federal regulation, a physician must have "the capacity to refer the patients for appropriate counseling and other appropriate ancillary services."[179,180] Addiction-focused Medical Management (see Addiction-focused Medical Management for more information) in OBOT typically combines monitoring of medication adherence and drug use through urine drug testing with brief counseling by the physician using MI and encouraging participation in mutual help programs (e.g., Alcoholics Anonymous [AA], Narcotics Anonymous [NA]) participation.

CM is a motivational intervention that uses behavioral reinforcement principles (such as providing vouchers, money, or other rewards) to encourage behavior change. Ling et al. found no positive effects for contingencies on the proportion of opioid negative urine test results over the number of tests possible, in a sample of patients receiving buprenorphine and medical management.[51] Conversely, two studies demonstrated that adding a computerized version of a behavior therapy approach known as Community Reinforcement Approach (CRA) may improve OBOT outcomes compared to providing CM alone [181] or standard care alone.[182] So-called "standard care" usually consists initially of medication treatment plus weekly, individualized, supportive counseling sessions that address psychosocial issues as experienced by each patient. In contrast, CRA is a cognitive behavioral approach that includes counseling in specific life skills (e.g., affect and behavioral regulation, psychosocial skills, drug-refusal) and practice exercises via standardized training modules. CRA has a solid base in evidence as reviewed by Bickel et al. (2008).[182] These modules, when used, are usually applied by therapists via live/in-person sessions. Computerized versions of CRA allow patients to work through the modules in an interactive fashion (i.e., they are not static "lessons"). There is evidence that adding either of these two approaches (in-person or computer-delivered) yields equivalent outcomes that are superior to treatment without CRA.[181,182] Importantly, the use of a computerized treatment program had no negative impact on therapeutic alliance (see section on Engagement Strategies).

Recommendation

15. In Opioid Treatment Program settings, we suggest offering individual counseling and/or Contingency Management, considering patient preferences and provider training/competence.
    (Weak For| Reviewed, New-replaced)

Discussion

OTPs provide OAT, most commonly methadone, according to the Code of Federal Regulations.[170] Research supports offering a variety of psychosocial interventions in combination with OAT.[183-185] Psychosocial interventions are typically introduced early and sustained throughout the course of OAT based on patient needs and preferences.

While methadone medication alone is effective in reducing illicit opioid use,[186] recovery is enhanced by providing standard methadone maintenance that includes individual counseling.[184,185] Enhanced methadone maintenance addresses additional psychosocial needs (i.e., vocational counseling, legal assistance) and provides psychotherapy to address co-occurring disorders. One small study suggests it may improve recovery outcomes when the services provided are directed specifically at the problem areas pertinent to each individual patient.[184] The Code of Federal Regulations requires that OTPs conduct a comprehensive biopsychosocial assessment and treatment plan that addresses each identified need. Subsequent clarification [170] and TJC standards require that OTPs provide psychosocial interventions similar to standard methadone maintenance as described by McLellan et al.[184]

A SR [187] and a clinical trial [188] found no significant difference in treatment retention for patients receiving standard methadone maintenance [184] versus the addition of another specific psychosocial intervention. Other opioid outcomes were not included. The authors noted that standard methadone maintenance provided substantial psychosocial interventions and cautioned that their results should not be interpreted to mean psychosocial interventions were not necessary. At least three well-designed, RCTs have studied this topic with clear and consistent findings.[184,189,190] Two of the studies compared medication only to medication with standard counseling and to enhanced services added to the standard condition.[184,189] One study compared standard counseling to a day treatment program.[190] The two studies that included medication only showed that adding standard counseling improved outcomes. Two of the studies found no differences in outcomes between standard counseling and enhanced services. One study found a benefit of enhanced services if those services were specifically directed to areas of identified need, but subsequently found that these additional services were not cost effective.[191] More recently, Kidorf et al. (2013) conducted a randomized trial evaluating the efficacy of CM to encourage attendance at psychiatric sessions. The intervention was aimed at improving the delivery of onsite and integrated psychiatric services in a sample of opioid-dependent outpatients with co-occurring psychiatric disorder receiving methadone in an OTP.[192] Although CM improved the utilization of psychiatric services within an OTP, there was no difference in psychiatric symptoms or percentage of opioid or cocaine positive urine tests obtained during the 12 week study or on self-reports of substance use between groups.[192] Similarly, Tuten et al. (2012) found no differences between escalating incentives, fixed incentives, or a control group where incentives were not tied to abstinence on opioid- or cocaine-positive urine test results.[188]

Recommendation

16. For patients with opioid use disorder for whom opioid use disorder pharmacotherapy is contraindicated, unacceptable or unavailable, there is insufficient evidence to recommend for or against any specific psychosocial interventions.
    (N/A | Reviewed, New-replaced)

Discussion

The evidence identified in the SR for this CPG primarily comprised studies in which patients received psychosocial intervention in conjunction with, or as an adjunct to, medication-assisted therapy. Epidemiologic data indicates a high mortality associated with OUD [193] and clinical trials indicate a high risk of relapse after opioid detoxification.[53] Therefore, there was insufficient evidence on the effectiveness of psychosocial interventions in the patient population who were not on medication-assisted therapy.

c. Cannabis Use Disorder

i. Pharmacotherapy

Recommendation

17. There is insufficient evidence to recommend for or against the use of pharmacotherapy in the treatment of cannabis use disorder.
    (N/A | Reviewed, New-added)

Discussion

Some patients seek pharmacologic assistance in cutting down or abstaining from marijuana use. However, no medication has been shown to be effective. Drug trials examining candidate therapies in the marijuana literature are characterized by small sample sizes (n=20-100), short duration (on the order of 12 weeks), high dropout rates (typically 50-70% by study end), and absence of treatment effect attributable to the intervention drug. Some form of psychotherapy was provided to both treatment and control groups, and intensity of marijuana usage declined in both groups at similar rates over the duration of the studies.

Four of five RCTs failed to show a primary treatment effect in the experimental drug group. This includes one study each for bupropion sustained-release,[194] nefazodone,[194] fluoxetine,[195] buspirone,[196] and atomoxetine.[197] Only a single gabapentin study demonstrated meaningful improvements in marijuana use and withdrawal symptoms, but the sample size was small (n=50);[198] additional corroborating studies are needed. Fluoxetine showed efficacy for depressive symptoms, but did not improve marijuana use measures.[195]

ii. Psychosocial Interventions

Recommendation

18. For patients with cannabis use disorder, we recommend offering one of the following interventions as initial treatment considering patient preference and provider training/competence:
    - Cognitive Behavioral Therapy
    - Motivational Enhancement Therapy
    - Combined Cognitive Behavioral Therapy/Motivational Enhancement Therapy

    (Strong For | Reviewed, New-replaced)

Discussion

A brief description of the evidence for the use of these interventions for patients with cannabis use disorder can be found below. Additional information about these interventions, as well as the appropriateness of their use for patients with specific types of SUD, can be found in Appendix C.

A SR of fair quality by Davis et al. (2015) assessed the efficacy of behavioral therapy (BT) in cannabis users.[199] Each study included Cognitive Behavioral Therapy (CBT) as one of the intervention groups. The BT intervention significantly outperformed the control group by 66% in pooled outcomes including frequency and severity of use and measures of psychosocial functioning. The effect sizes of BT were greater compared to waitlist controls and active controls (e.g., those who received case management alone). BT alone did not significantly outperform active controls, and abstinence rates were low in both groups. The quality of evidence was rated moderate compared to waitlist. An earlier multisite trial found that among patients with cannabis dependence, two sessions of Motivational Enhancement Therapy (MET), did not reduce marijuana use over 15-month follow-up as much as a nine-session multicomponent intervention that also included CBT and case management.[200]

There is insufficient evidence for or against recommending any other specific psychosocial interventions for cannabis use disorder; however there is preliminary work on patients with cannabis use disorder and co-occurring mental health conditions. A fair quality SR by Hjorthoj et al. (2014) studied interventions targeting cannabis use disorder in patients with schizophrenia spectrum disorders.[201] They evaluated the effect of motivational interviewing (MI) with or without CBT versus control (TAU), routine family support, or psychoeducation). In terms of consumption, MI, when compared to control, significantly reduced the amount of cannabis used but not the frequency of use.

Brief MI/CBT in patients with a DSM-IV diagnosis of cannabis use dependence or abuse and non-affective psychotic disorder was studied in comparison to long MI/CBT versus standard of care.[202] Low quality evidence found no significant differences between MI/CBT and TAU in abstinence, relapse of psychotic symptoms, days to relapse, or hospitalization outcomes at various time points. In a study by Kay-Lambkin et al. (2011) participants with cannabis use disorder and depression received either therapist or computerized-delivered CBT/MI or person-centered therapy (PCT).[203] The analysis found no difference by treatment groups in change in cannabis use, abstinence, or percent of patients achieving a ≥50% reduction in use.

d. Stimulant Use Disorder

i. Pharmacotherapy

Recommendation

19. There is insufficient evidence to recommend for or against the use of any pharmacotherapy for the treatment of cocaine use disorder or methamphetamine use disorder.
    (N/A | Reviewed, New-added)

Discussion

Evidence does not support the use of indirect dopamine agonist therapy (e.g., disulfiram, modafinil, bupropion, methylphenidate, dexamphetamine, mixed amphetamine salts), doxazosin, or topiramate for the treatment of cocaine use disorder or methamphetamine use disorder. A number of small studies have shown

mixed results with some studies showing modest benefits, while a number have shown no benefit.[204,205] Further complicating the situation, there is evidence that disulfiram at some doses worsens cocaine use disorder while at a dose of 250 mg/day, cocaine use decreases.[205-207] Further research into the use of dexamphetamine to treat methamphetamine use disorder is needed, as an initial study showed that its use increased participation in treatment while not decreasing use.[208] Given the potential misuse of dexamphetamine, the authors cannot recommend its use without further evidence.

Given the wide variation in the results of the studies, we have little confidence in the evidence to guide treatment either for or against the use of indirect dopamine agonist therapy for either cocaine or stimulant use disorder. Given the absence of clear evidence of benefit, clinicians must consider other implications specific to the medication. For instance, the likelihood of misuse and diversion in patients receiving methylphenidate, dexamphetamine, and mixed amphetamine salts should be considered.

A small number of RCTs have explored the use of topiramate to decrease cocaine use. One study showed a decrease in use,[209] while two other studies showed no difference in cocaine use.[210,211] One study showed that there were no significant differences in rate of abstinence in methamphetamine use disorder with use of topiramate compared to placebo.[212]

ii. Psychosocial Interventions

Recommendation

20. For patients with stimulant use disorder, we recommend offering one or more of the following interventions as initial treatment considering patient preference and provider training/competence:
    - Cognitive Behavioral Therapy
    - Recovery-focused behavioral therapy
        - General Drug Counseling
        - Community Reinforcement Approach
    - Contingency Management in combination with one of the above

    (Strong For| Reviewed, New-replaced)

Discussion

A brief description of the evidence for the use of these interventions for patients with stimulant use disorder can be found below. Additional information about these interventions, as well as the appropriateness of their use for patients with specific types of SUD, can be found in Appendix C.

Cognitive Behavioral Therapy (CBT) has been found to be effective for the treatment of cocaine use disorder.[213-215] In addition, individual drug counseling, which is based on a 12-step addiction treatment model, improved outcomes over group drug counseling only and was also superior to cognitive therapy and a psychodynamic approach in one large, multi-site study.[216]

Contingency Management (CM) has the strongest evidence of effectiveness for cocaine use disorder, when used adjunctive to another psychosocial intervention.[213,217,218] Another recent SR found CM to be consistently more effective than CBT during treatment, with less evidence of superiority during post-treatment follow-ups.[219] Extending the duration in which reinforcement for abstinence is provided extends the positive effects of CM,[220] but positive effects generally deteriorate fairly rapidly after the

intervention has ended in most, but not all, studies. For example, Higgins et al. (2000) found evidence of sustained positive effects for 12 months after the end of CM.[221] Treatment effects are generally much larger when abstinence, as opposed to attendance, is reinforced, although this may not be the case with better-prognosis patients who are cocaine abstinent when they enter treatment.[222] Higher monetary value reinforcers produce higher rates of cocaine abstinence,[223] particularly in those with more severe cocaine problems.[222] Prize-based CM interventions, in which the amount of the reinforcement varies by chance, may be more cost-effective than fixed-value reinforcement.[224,225]

The Community Reinforcement Approach (CRA), a comprehensive intervention that combines CBT, couples counseling, and other recovery focused components, as well as CM in some cases, has outperformed comparison conditions (e.g., 12-step counseling, drug counseling, and CRA without voucher incentives), in several studies.[226-228] In some studies the combination of CM and other behavioral interventions, such as CRA or CBT, has been more effective than comparison conditions.[213,229] For example, Higgins et al. (2003) found that the combination of CRA and CM produced better within-treatment cocaine use outcomes than CM only, as well as fewer days of heavy drinking, better employment outcomes, lower depression, and fewer medical hospitalizations during treatment and a post treatment follow-up.[226]

There is considerably less evidence concerning effective treatments for other stimulant disorders. One SR found that behavioral interventions, including CBT, CBT plus motivational interviewing (MI), and MI, were not more effective than passive or minimal interventions with regard to non-cocaine stimulant consumption outcomes. However, high intensity or adjunctive treatments, such as gay-specific CBT, CM plus CBT, CM plus TAU, and CM plus placebo, did produce better stimulant use outcomes than single active treatments (CBT or TAU).[230] It should be noted that most of these high intensity interventions included CM, so the positive effect identified may really be for CM over other active behavioral interventions.

Confidence in the quality of the evidence regarding the effectiveness of these interventions for the treatment of cocaine and other stimulant use disorders is moderate for CM interventions, and low-to-moderate for other behavioral interventions, with benefits outweighing harms and burdens and some variations in patient values and preferences. Primary concerns regarding use of these interventions include the considerable training to implement with fidelity (CBT and CRA) and the resource intensive delivery (CM, CBT, and CRA). CM, for example, requires the collection and rapid analysis of 2-3 urine samples per week, plus timely feedback on the results. However, a recent large-scale demonstration project has indicated that CM is feasible to deliver within VA SUD treatment programs.[231] Finally, the research evidence is based almost entirely on studies in which these interventions were delivered individually to patients, whereas most SUD treatment in the VA and DoD is delivered in groups.

E. Promoting Group Mutual Help Involvement

Recommendation

21. For patients with substance use disorders in early recovery or following relapse, we recommend promoting active involvement in group mutual help programs using one of the following systematic approaches considering patient preference and provider training/competence:
    - Peer linkage

- Network support
- 12-Step Facilitation

(Strong For | Reviewed, New-replaced)

Discussion

Several effective interventions have been developed to increase attendance at and participation in mutual help programs and other recovery oriented social support programs. The first of these is 12-Step Facilitation (TSF) which is delivered over 12 sessions and is focused on helping participants complete the first five steps of the Alcoholics Anonymous (AA) program. TSF fosters regular attendance at mutual help meetings and active participation in the programs, including speaking at meetings, obtaining a sponsor, using the telephone to get support, and participating in social activities outside of the meetings.[232] In a sample of individuals with co-occurring SUD and major depression, TSF led to higher attendance at and participation in mutual help programs than Cognitive Behavioral Therapy (CBT) during the 24-week treatment phase.[233,234] However, there were no differences between the two interventions on group mutual help variables in the year following treatment.

A three-session peer linkage intervention focused on increasing attendance at mutual help meetings.[235] This intervention consisted of information about the 12-step approach to recovery, contracting to attend mutual help meetings, linkage with a peer in a 12-step program with whom the participant could attend meetings, monitoring of 12-step meeting attendance, and help in obtaining a temporary sponsor. Results indicated that patients randomized to this enhanced referral condition had higher rates of 12-step meeting attendance and program involvement over the 12-month follow-up than those randomized to standard referral.[235,236] Moreover, the peer linkage referral condition also produced higher abstinence rates over the follow-up than standard referral.[236]

Litt et al. (2007) adapted the TSF intervention to develop Network Support (NS), which stresses changing one's broader social network to be more supportive of abstinence, as well as advocates involvement in 12-step programs.[237] AA philosophy and focus on a higher power are de-emphasized in this 12-session intervention, in favor of AA as a means to make new friends and increase involvement in enjoyable social activities that would make abstinence more reinforcing. Other social network programs were explored, particularly for patients who will not attend mutual help programs. Results of an RCT comparing NS to case management found increased social support for abstinence, through an increase in abstinent friends, relative to case management.[237] With regard to mutual help attendance, those in NS were over seven times more likely to attend AA over the 15-month follow-up than those in case management. Analyses of 24-month outcomes confirmed that the positive effect of NS on AA attendance, relative to case management, was sustained.[238]

Confidence in the quality of the evidence regarding the effectiveness of interventions to increase participation in mutual help organizations and other recovery oriented social supports is moderate, with benefits outweighing harms and burdens, and variations in patient values and preferences. Evidence has primarily focused on use of these interventions in the short-term. Counter-therapeutic advice from peer-led resources is a potential harm in using systematic interventions to increase the participation of patients and their families to mutual help programs. Potential burdens include difficulty for some patients in tolerating group meetings (e.g., those with PTSD or social anxiety disorder), potential travel costs and

accessibility issues. Patient values and preferences should always be considered in developing treatment options and in referring to mutual help programs.

In order for providers to discuss the potential benefits of mutual help groups and other recovery oriented social supports with their patients, providers need to know about these programs and the differences between them. Moreover, it is advisable to have information on location and scheduling of local meetings available.[239]

F. Co-occurring Mental Health Conditions and Psychosocial Problems

Recommendation

22. Among patients in early recovery from substance use disorders or following relapse, we suggest prioritizing other needs through shared decision making (e.g., related to other mental health conditions, housing, supportive recovery environment, employment, or related recovery-relevant factors) among identified biopsychosocial problems and arranging services to address them. **(Weak For | Not reviewed, Amended)**

Discussion

Many patients with SUD have co-occurring psychosocial problems that affect their likelihood of establishing and maintaining good clinical outcomes and improved functional status. Some of these problems are consequences of SUD that persist even after early recovery is established. Others occur independently of SUD, but can complicate access to care or present relapse risk. These problems include co-occurring mental health conditions, access to a supportive recovery environment (housing and social support for sobriety), difficulties with family and social relationships, unemployment/underemployment, and/or unresolved legal issues. Patients are likely to have individual priorities for when and how these needs are addressed. However, these issues are often related and interact with one another, and they can be difficult to prioritize. Although it may be optimal to have services coordinated by a single treatment team, there is likely to be variability in the extent of comprehensive services available in different clinical settings.

Fair quality evidence reviewed in the prior version of the guideline indicates targeting individualized services for identified problem areas is more effective than routinely increasing the intensity of addiction-focused psychosocial treatment alone.[240-242] An important consideration is providing adjunctive recovery services in the least restrictive setting that promotes engagement in continuing addiction care (e.g., via transitional housing that improves access to treatment, accommodating employment schedules and other service appointments). For practical purposes, it is common to defer attention to some initially identified problems and monitor for emerging clinical needs until early recovery has stabilized.

G. Follow-up

Recommendation

23. We suggest assessing response to treatment periodically and systematically, using standardized and valid instrument(s) whenever possible. Indicators of treatment response include ongoing substance use, craving, side effects of medication, emerging symptoms, etc. **(Weak For | Reviewed, New-replaced)**

Discussion

Measurement-based care is the periodic and systematic assessment of response to treatment, using standardized and valid instrument(s) whenever possible.[243,244] Periodic monitoring of patients' progress offers patients and providers the opportunity to identify barriers to adequate progress on problems identified at intake and any new problems that emerge, thereby facilitating needed changes in treatment strategies. Periodic intervals for follow-up or monitoring may include, but are not limited to:

- At agreed upon milestones during treatment
- At discontinuation or change in intensity of specialty care
- Based on laboratory or other monitoring
- If patient is non-adherent

Although there was insufficient evidence to make a recommendation for or against measurement-based care in either primary or specialty care settings for improving consumption and health outcomes, there are a number of benefits to consider which include:

- Patient accountability ("No one will know" is a common trigger for relapse)
- Continual feedback and monitoring of treatment response
- Compliance with accrediting expectations of outcome evaluation

When indicated, management should be adjusted to optimize treatment outcomes. There is large variation in patient and provider preferences that should be taken into consideration when planning which outcomes to measure with what methods and how frequently. Other implications to consider when customizing care may include patient acceptability, resource use, feasibility, and administrative workload.

Recommendation

24. For patients who have initiated an intensive phase of outpatient or residential treatment, we recommend offering and encouraging ongoing systematic relapse prevention efforts or recovery support individualized on the basis of treatment response.
    (Strong For | Not reviewed, Amended)

Discussion

Clinicians commonly emphasize that many or most patients in SUD treatment will benefit from continuing care ("aftercare") after participating in a more intensive, initial phase of treatment. The National Institute on Drug Abuse (NIDA) has also stressed that retaining patients for longer treatment durations, in particular 90 days or more, is more likely to lead to successful outcomes.[245] A meta-analysis of 19 controlled studies found that continuing care had a small but significant positive effect on substance use outcomes over no/minimal continuing care at the end of the intervention and at follow-up.[246]

Although there had been some evidence in prior narrative reviews that continuing care interventions were more likely to be effective when they were at least 12 months in duration and included more active efforts to deliver the intervention to patients,[247] the Blodgett et al. (2014) meta-analysis did not find that continuing care effects varied by intervention duration, intensity, modality, or setting.[246] Therefore, the selection of appropriate continuing care should be made on the basis of patient preference and the

availability of treatment options, using evidence-based SUD interventions whenever possible. Continuing care efforts should be directed at preventing relapse and limiting the severity of relapses that do occur, and should address other issues that can interfere with recovery, as needed. Services can be provided via individual or group sessions in the clinic, with some evidence that effective continuing care can also be provided over the telephone.[248-250]

Given the findings of the Blodgett et al. (2014) review,[246] confidence in the quality of the evidence for this recommendation is moderate to high. Because extended participation in treatment does confer some burden to patients, and the positive effects appear to be small overall, the benefits are seen as slightly outweighing the harms or burdens. There is large variation in patient willingness to engage in continuing care. Moreover, accessibility can be an issue in more rural areas and for Veterans with disabilities or other issues that make travel to a treatment program more difficult. For such patients, telephone continuing care may be considered.

Recommendation

25. For patients in substance use disorders specialty care, we recommend against automatic discharge from care for patients who do not respond to treatment or who relapse.
    (Strong Against | Not reviewed, Amended)

Discussion

Relapse during the course of SUD treatment is common, even for patients who are receiving effective, evidence-based interventions. Moreover, some patients who eventually abstain do not achieve abstinence early in treatment. At one point, it was common practice in SUD treatment programs to continue to provide standard, unmodified care to such patients or to discharge them. However, it may be possible to improve the outcomes of treatment non-responders by retaining them in care and modifying their treatment in some way. For example, there is some evidence that patients who make poor progress toward achieving their goals with intensive outpatient treatment, particularly those who fail to stop using alcohol or cocaine, will have better substance use outcomes if they receive either more intensive, face-to-face [249] or extended [250,251] continuing care. On the other hand, some patients who are not responding may benefit from a lower intensity treatment approach, if they find the current level of care too burdensome. Lower intensity engagement strategies also provide the opportunity to monitor patient readiness for involvement in more intensive or other treatment interventions to promote recovery.

It has become standard practice in most areas of medicine to regularly and systematically monitor response to treatment and, on the basis of patient response, make modifications to care as needed over time. Although there is not a strong empirical base for this approach in SUD treatment at this point, there is expert consensus to support it.[252,253] Therefore, rather than discharge patients who have not responded to treatment, or who responded initially but subsequently resumed problematic substance use, we suggest providers consider modifying treatment in one of the following ways:

- Add or substitute another medication or psychosocial intervention, and/or
- Change treatment intensity by:
    - Increasing the intensity of care, or
    - Adjusting the dose of the medication, or

- Decreasing the intensity to a minimum level of care that is agreeable to the patient, such as monitoring in general healthcare.

Given the lack of a strong empirical base demonstrating the efficacy of this approach over more traditional treatment models, confidence in the quality of the evidence is very low. Further research is needed to compare the risks and benefits of administrative discharge from care and of various models of adjusting care based on response to treatment. However, the benefits of retaining patients in treatment and modifying their care in an effort to improve response or acceptability clearly outweigh harms or burdens to the patient. One important consideration is that retaining non-responding patients and modifying their treatment as needed can require additional staff time and effort. Clinics may have limited resources to support the availability of a menu of other interventions for non-responders. Finally, some non-responders are simply not interested in further addiction-focused treatment of any kind at that point in time, regardless of efforts made to retain them or treatment options made available.

H. Stabilization and Withdrawal

a. Assessment

Recommendation

26. For patients with alcohol or opioid use disorder in early abstinence, we suggest using standardized measures to assess the severity of withdrawal symptoms such as Clinical Institute Withdrawal Assessment for Alcohol (revised version) (CIWA-Ar) for alcohol or Clinical Opiate Withdrawal Scale (COWS) for opioids.
(Weak For | Not reviewed, Amended)

Discussion

Standardized scales to quantify the severity of alcohol and opioid withdrawal have been developed for clinical and research purposes to aid in the diagnosis of withdrawal, to indicate the need for medications, and to predict severity of alcohol withdrawal and need for intensive care.[254] In research settings, such scales aid in comparing clinical trial outcomes; in clinical settings, they may improve patient safety through assuring systematic assessment and symptom-guided administration of medication.[254-257]

For assessing alcohol withdrawal, the CIWA-Ar is perhaps the most widely adopted standardized scale.[254,256,258] This is due in part to its ability to meet all three purposes for standardized withdrawal assessment. It has validity and interrater reliability in assessing the severity of alcohol withdrawal, is relatively quick to administer (about one minute for trained administrators), and is able to distinguish alcohol withdrawal symptoms in patients whose vital signs are elevated due to concurrent medical illnesses, such as infections and cardiovascular disease, rather than due to withdrawal itself.[259,260] It can help predict those patients at risk for more complicated alcohol withdrawal.[254,255,261] Its use in determining need for medication in symptom-triggered protocols is associated with lower total dose of benzodiazepines and shorter lengths of hospital stay.[257,262] Its incorporation as part of an emergency department protocol for assessment of alcohol withdrawal risk was associated with fewer inpatient admissions for management of alcohol withdrawal.[263]

While the CIWA-Ar has been widely adopted, several investigators have sought modifications or alternative scales to address several specific shortcomings. While the CIWA-Ar is quicker to administer

than many of its predecessors, some investigators have cited the need for staff training and time for administration as barriers to its use in many clinical settings.[254] Gossop et al. (2002) developed the 10-item Short Alcohol Withdrawal Scale (SAWS) which demonstrates good interrater reliability and correlation with CIWA-Ar.[264] Reoux and Oreskovich (2006) modified the CIWA-Ar to include additional alcohol withdrawal symptoms from the DSM-IV-TR that are not covered in the CIWA-Ar and to eliminate items that were not in the DSM-IV diagnostic criteria for alcohol withdrawal.[258] The resulting seven-item CIWA-AD agrees closely with the CIWA-Ar.[258]

CIWA-Ar does not predict risk of complicated alcohol withdrawal in patients before the onset of alcohol withdrawal syndrome (AWS). In a case-control retrospective chart review of general medical inpatients, Pecoraro et al. (2014) used the routinely administered Alcohol Use Disorders Identification Test-Primary Care (AUDIT-PC), a screening tool for alcohol misuse, to determine a score that predicted alcohol withdrawal or alcohol withdrawal delirium by International Classification of Diseases, Ninth Revision discharge diagnosis. An AUDIT-PC score of four or more was associated with predicted AWS with 91.0% sensitivity and 89.7% specificity, identifying 17 false positives for every true positive.[265] Wetterling et al. (2006) developed the Luebeck Alcohol Withdrawal Risk Scale-11 (LARS-11), on which a score of 10 or higher can be used to predict at hospital admission which patients would require close medical attention.[266] The positive predictive value for severe AWS was 76%, while the negative predictive value was 98.7%. The sensitivity and specificity for LARS-11 were high at 95% and 92.5%, respectively.[266] Stephens et al. (2014) developed an emergency department protocol for assessment of alcohol withdrawal risk that included the CIWA-Ar, blood alcohol level (BAL), vital signs, assessment of concurrent medical conditions, and history of withdrawal seizures and delirium tremens. By systematically applying the resulting algorithm, they decreased the number of inpatient admissions for alcohol withdrawal without increasing patient returns to the emergency department for treatment of alcohol withdrawal.[263] In a SR of the literature, Goodson, Clark, and Douglas (2014) identified a previous history of delirium tremens or alcohol withdrawal seizures as the strongest predictors of subsequent complications.[267] Maldonado et al. incorporated history of delirium tremens and alcohol withdrawal seizures into a 10-item screening questionnaire, the Prediction of Alcohol Withdrawal Severity Scale (PAWSS), to predict moderate to severe alcohol withdrawal. A PAWSS score ≥4 demonstrated 93.1% sensitivity and 99.5% specificity with a positive predictive value of 93.1% and a negative predictive value of 99.5% in a prospective validation study of 409 medical inpatients.[268] While the PAWSS demonstrated excellent predictive value for medical inpatients, more research is needed to determine its predictive value in other populations such as psychiatric inpatients and those seeking outpatient or residential treatment of SUD.

Similarly, investigators have sought reliable, valid, and practical systematic assessment tools for opioid withdrawal. Handelsman et al. (1987) developed the 16-item Subjective Opiate Withdrawal Scale (SOWS) and the 13-item Objective Opiate Withdrawal Scale (OOWS) as brief and practical alternatives to the 73-item Addiction Research Center Inventory-Weak Opiate Withdrawal Scale.[269] Wesson and Ling (2003) developed the 11-item clinician-administered COWS to assess for precipitated opioid withdrawal in patients starting treatment with buprenorphine.[270] The COWS was subsequently validated against a longer, but validated, research scale, the Clinical Institute Narcotic Assessment Scale.[271]

While many scales have been developed to assist in systematic assessment of alcohol and opioid withdrawal, and there is evidence for benefit in terms of shortening length of hospital stay, reducing

amount of sedative medications, and averting unnecessary hospitalization, there have been no randomized, controlled comparisons of the outcome of alcohol or opioid withdrawal treatment with and without systematic assessments. Further research is needed to define the risks and benefits of systematic assessment scales and decision support tools for withdrawal treatment in common treatment settings such as inpatient psychiatry units, residential SUD treatment programs and outpatient general mental health, general medicine, and specialty SUD treatment clinics.

Recommendations

27. We recommend inpatient medically supervised alcohol withdrawal management for patients with any of the following conditions:
    - History of delirium tremens or withdrawal seizures
    - Inability to tolerate oral medication
    - Co-occurring medical conditions that would pose serious risk for ambulatory withdrawal management (e.g., severe coronary artery disease, congestive heart failure, liver cirrhosis)
    - Severe alcohol withdrawal (i.e., Clinical Institute Withdrawal Assessment for Alcohol [revised version] [CIWA-Ar] score ≥20)
    - Risk of withdrawal from other substances in addition to alcohol (e.g., sedative hypnotics)

    (Strong For | Reviewed, Amended)

28. We suggest inpatient medically supervised withdrawal for patients with symptoms of at least moderate alcohol withdrawal (i.e., Clinical Institute Withdrawal Assessment for Alcohol [revised version] [CIWA-Ar] score ≥10) and any of the following conditions:
    - Recurrent unsuccessful attempts at ambulatory withdrawal management
    - Reasonable likelihood that the patient will not complete ambulatory withdrawal management (e.g., due to homelessness)
    - Active psychosis or severe cognitive impairment
    - Medical conditions that could make ambulatory withdrawal management problematic (e.g., pregnancy, nephrotic syndrome, cardiovascular disease, lack of medical support system)

    (Weak For | Reviewed, Amended)

Discussion

AWS includes: insomnia, autonomic symptoms, increased hand tremors, nausea and/or vomiting, psychomotor agitation, anxiety, seizures, and hallucinations. There are also specific potential harms (including death) associated with severe AWS and, in the presence of other risk factors, moderate AWS. A patient's history of delirium tremens, previous episodes of AWS, and co-occurring medical conditions are all commonly accepted as indications for inpatient medically supervised alcohol withdrawal.

Moreover, while patients are more likely to successfully complete an inpatient medically supervised alcohol withdrawal protocol, long-term alcohol withdrawal outcomes do not differ between those in inpatient or outpatient programs.[272,273] Other factors to consider when determining inpatient or outpatient medically supervised alcohol withdrawal include:[274]

Ambulatory withdrawal management has the potential advantages of:

- Facilitating continuity of care in the outpatient setting
- Reducing disruption to the patient's life
- Lowering costs

Inpatient withdrawal management has the advantages of:

- Having fewer medical and legal logistical concerns (e.g., arranging for patient transportation, driving during the course of medically supervised withdrawal)
- Allowing closer monitoring of AWS
- Providing complex addiction-focused Medical Management (see Addiction-focused Medical Management for additional information) of AWS and co-occurring medical conditions (e.g., cardiac monitoring, intravenous hydration, medications)
- Having higher likelihood of completing the AWS management protocol

b. Alcohol Use Disorder Stabilization and Withdrawal

Recommendation

29. We recommend using one of the following pharmacotherapy strategies for managing alcohol withdrawal symptoms:
    - A predetermined fixed medication tapering schedule with additional medication as needed
    - Symptom-triggered therapy where patients are given medication only when signs or symptoms of withdrawal occur (e.g., as needed dosing)

    (Strong For | Not reviewed, Amended)

Discussion

Strong evidence supports both of the above approaches to the management of acute alcohol withdrawal. In the fixed dose approach, medication is given in advance of the emergence of anticipated withdrawal signs and symptoms. The advantages of a fixed-dose approach with additional medication as needed are that the patient will likely receive sufficient medication to prevent the emergence of alcohol withdrawal signs and symptoms and that the level of clinical monitoring needed may be somewhat less than with the symptom-triggered approach. The disadvantage of the fixed-dose approach is that, since it is challenging to predict the severity of alcohol withdrawal for any given patient, the patient may receive more medication than is actually needed and could incur side effects from the medications used to treat withdrawal.

The advantage of the symptom-triggered approach is that the patient only receives the amount of medication needed to manage alcohol withdrawal during that specific episode of care. However, the symptom-triggered approach does require skilled staff to assess severity of alcohol withdrawal frequently using a validated measure (typically the CIWA-Ar).

One randomized, double-blind trial of fixed-dose versus symptom-triggered treatment was completed with Veterans on an inpatient unit.[275] The symptom-triggered group had a significantly shorter duration of treatment and used significantly less chlordiazepoxide during withdrawal. Another double-blind randomized trial comparing these two approaches conducted in Switzerland and using oxazepam had similar findings with the exception that one patient in the symptom-triggered condition had a withdrawal-related seizure.[276] Other observational studies generally support these findings.[262,277] Clinicians need to consider staffing and patient characteristics when weighing risks of complicated withdrawal versus benefits of shorter length of hospital stay associated with symptom-triggered withdrawal.

Recommendation

30. For treatment of moderate to severe alcohol withdrawal, we recommend using benzodiazepines with adequate monitoring because of documented efficacy and high margin of safety. **(Strong For | Reviewed, Amended)**

Discussion

Strong evidence involving numerous controlled trials supports the use of benzodiazepines in the treatment of Alcohol Withdrawal Syndrome (AWS).[278,279] Compared to placebo, benzodiazepines reduce withdrawal severity, incidence of delirium, and withdrawal seizures. Benzodiazepines are the drug of choice, given adequate monitoring, because they reduce withdrawal severity, incidence of delirium, and seizures. Benzodiazepines are generally well tolerated, although some sedation can occur.

Although a few small RCTs also support the efficacy of anticonvulsants (e.g., gabapentin, carbamazepine, valproic acid) in the treatment of alcohol withdrawal,[278,280-282] the body of evidence at this time is not sufficient to recommend these agents as first-line treatments. In particular, it is not clear that these agents are as efficacious in preventing alcohol withdrawal seizures as are benzodiazepines.

Recommendation

31. For managing mild to moderate alcohol withdrawal in patients for whom risks of benzodiazepines outweigh benefits (e.g., inadequate monitoring available, abuse liability, or allergy/adverse reactions), we suggest considering carbamazepine, gabapentin, or valproic acid as an alternative. **(Weak For | Reviewed, New-replaced)**

Discussion

In cases for which risks of benzodiazepines outweigh benefits, the anticonvulsants gabapentin, carbamazepine, and valproic acid appear to be reasonable alternative agents for management of alcohol withdrawal.[278,280-282] Although the studies to date examining these medications have been primarily small single site randomized trials, the evidence available suggests that outcomes, such as reduction of withdrawal symptoms, time to withdrawal completion, and adverse events, are generally equivalent with these anticonvulsants and benzodiazepines. However, it is not entirely clear if these medications are equivalent to benzodiazepines for preventing withdrawal delirium or withdrawal seizures where there is elevated risk.

These agents may have particular utility for ambulatory medically supervised withdrawal when concerns exist about the prescribing of a controlled substance such as a benzodiazepine. Furthermore, valproic acid can also be used as an effective supplement to benzodiazepines.

Recommendation

32. We recommend against using alcohol as an agent for medically supervised withdrawal. **(Strong Against | Not reviewed, Amended)**

Discussion

Alcohol itself is still used by some practitioners to treat AWS.[283,284] No solid evidence exists, other than clinical experience, to support this practice. One small RCT conducted in an intensive care unit compared prophylactic treatment with an intravenous alcohol infusion to prophylactic treatment with diazepam.[285] No advantages were found with alcohol compared to diazepam. More patients treated with alcohol exhibited inadequate sedation. One patient on the ethanol regimen failed treatment and had to be protectively transferred to a diazepam regimen.

Since alcohol has a very short duration of action, it is more likely to cause respiratory depression than are benzodiazepines. It can have proconvulsant effects and is damaging to many organ systems. Furthermore, no convincing rationale supports the use of alcohol to treat alcohol withdrawal when a safer and more effective alternative, benzodiazepines, is available.[286]

c. Opioid Use Disorder Stabilization and Withdrawal

Recommendation

33. For patients not yet stabilized from opioid use disorder, we recommend against withdrawal management alone due to high risk of relapse and overdose (see Recommendations 8 and 11). **(Strong Against | Reviewed, New-replaced)**

Discussion

For the treatment of opioid use disorder (OUD), for patients who are not stabilized, administration of long-term opioid agonists are generally preferred over short tapers of opioid agonists in “detoxification” protocols. Most patients who are provided detoxification, particularly those who do not receive formal, structured non-pharmacotherapy treatment, relapse with resultant morbidity and mortality.[287,288] Furthermore, opioid agonist therapies have been shown to be more effective than other pharmacotherapies over time and are likely safer.[289,290] Methadone has been used effectively over long periods of time for decades. Studies have also shown buprenorphine to be used successfully in office-based settings over long periods (years).[152-154,291] In addition, recent studies have shown that long term treatment, versus a quick taper, of patients with buprenorphine are more effective in achieving positive patient outcomes.[137]

There are certain situations where medically supervised withdrawal from opioids is preferred over long-term opioid agonist therapy (OAT). For instance, short taper of opioids using methadone, buprenorphine, or other symptom-treatment medications can be used if patients are (1) entering an environment which requires abstinence from any opioids (e.g., prison, some addiction treatment programs), (2) wish to receive non-opioid agonist treatment (e.g., treatment with injectable naltrexone), (3) have minimal

symptoms of physical opioid dependency, and (4) are in a profession that requires no opioid agonist treatments (e.g., military, healthcare provider, air traffic controller). Buprenorphine can be used to provide relatively short, safe, medically supervised withdrawal treatment.[292-298] There is no consensus on the treatment duration (e.g., 7- versus 28-day or 5- versus 30-day) for short term medically supervised withdrawal from opioids.[299,300] Recently, one randomized, double blind study found that a four-week buprenorphine taper was superior to a one-week or two-week taper for the outcome measure of opioid-negative urine drug screens.[151]

Recommendation

34. Among patients with opioid use disorder for whom maintenance agonist treatment is contraindicated, unacceptable, or unavailable, we recommend using a methadone (in Opioid Treatment Program only) or buprenorphine taper for opioid withdrawal management (see Recommendation 11).
    (Strong For | Reviewed, New-replaced)

35. For patients with opioid use disorder for whom methadone and buprenorphine are contraindicated, unacceptable, or unavailable, we recommend offering clonidine as a second-line agent for opioid withdrawal management (see Recommendation 11).
    (Strong For | Reviewed, New-replaced)

Discussion

The preferred approaches for medically supervised opioid withdrawal are initial stabilization with methadone or buprenorphine followed by a short or extended taper. Patient preferences play an important role in medication selection. The stigma of Opioid Treatment Programs (OTPs) may prevent a patient from choosing this option. In addition, access to care in OTPs and/or buprenorphine (from a provider with the appropriate DEA authorization) should be considered. According to the federal regulation, a physician must have "the capacity to refer the patients for appropriate counseling and other appropriate ancillary services."[179,180]

Treatment completion is one metric of success and has been evaluated by a number of RCTs. One study concluded that there are no significant differences in treatment completion with methadone versus buprenorphine; however, methadone was found to be superior to placebo in one study.[287] Three RCTs concluded that buprenorphine may be more effective than methadone.[296] In addition, buprenorphine and methadone were found to be more effective than clonidine.[296] Finally, one study was suggestive of no significant difference between methadone over clonidine in terms of treatment completion.[287] We found no evidence to support addition of clonidine to a regimen of buprenorphine or methadone.

Clonidine may be considered as a second line agent for symptom relief during inpatient medically supervised opioid withdrawal. Outpatient success is lower. If using clonidine, adjuvant medications for anxiety, restlessness, insomnia, muscle aches, nausea, and diarrhea may also be prescribed. Caution should be exercised when using clonidine as a second line agent, as it is associated with a decrease in systolic and diastolic blood pressure with resultant dizziness on standing compared to methadone.[301] Extra caution should be exercised in patients older than 50 due to the risk of dizziness and falling as well as

in those patients who are prone to hypotension. In addition to decreased blood pressure, clonidine is associated with dysphoria.[302,303]

d. Sedative Hypnotic Use Disorder Stabilization and Withdrawal

Recommendation

36. For patients in need of withdrawal management for sedative hypnotics, we suggest one of the following:
    - Gradually taper the original benzodiazepine
    - Substitute a longer acting benzodiazepine then taper gradually
    - Substitute phenobarbital for the addicting agent and taper gradually

    (Strong For | Reviewed, New-replaced)

Discussion

Benzodiazepine discontinuation is associated with a characteristic triad of symptoms: recurrence, rebound, and withdrawal. While the pattern and intensity of recurrent symptoms often resemble those of the original illness, rebound symptoms may be more intense and withdrawal symptoms may be severe and debilitating. Optimal clinical management of benzodiazepine discontinuation, including avoidance of abrupt drug discontinuation, can lessen withdrawal symptoms and promote successful drug discontinuation or dose reduction.[304]

The recommended clinical approach to benzodiazepine discontinuation is gradual dose tapering. Little data exists on the optimal rate of withdrawal; optimal duration of withdrawal may vary from patient to patient. The early stages of withdrawal are easier to tolerate than later stages so tapering schemes usually start with early rapid step-down in dose followed by a slower rate of reduction.[304] Low dose use of benzodiazepines can be tapered by 20% per week; however, higher dose benzodiazepine withdrawal should be conducted over an 8 to 12 week period, and up to six months should be allowed in exceptional cases.[304] A commonly used slow tapering strategy in a higher dose patient: weekly 25% dose reduction until 50% of the dose remains, followed by a one-eighth dose reduction every four to seven days.[305] Slow tapering schedules are associated with total cessation of benzodiazepine use in about two-thirds of patients.[304]

Substitution of a short-acting benzodiazepine with a longer acting agent such as diazepam or chlordiazepoxide is a common strategy designed to promote a smoother reduction of drug levels over time. A conversion chart (Table B-3) is used to determine the equivalent dose of the long-acting agent (which may be significantly higher than anticipated) and the slow taper is conducted as described above.

Phenobarbital can also be substituted for the dependent substance and gradually tapered. The average daily sedative-hypnotic dose is converted to a phenobarbital equivalent and divided into three doses per day for two days; beginning on day three, the phenobarbital dose should be reduced by 30 mg/day.

Management of benzodiazepine withdrawal and patient outcomes can be improved when extended tapering interventions take place in a structured clinical environment which includes close monitoring, optimized patient instruction/education, and Cognitive Behavioral Therapy (CBT).[306,307] Patients should

be monitored throughout the tapering period for withdrawal symptoms as well as for the disorder being treated; emergence of severe withdrawal symptoms signals a need to slow the tapering process.

VII. Knowledge Gaps and Recommended Research

As indicated throughout the CPG and in the sections below, further evidence is needed in particular areas of management for SUD. The items listed below are selected examples of gaps in knowledge. Organizations such as the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA) put forth strategic plans which also can be used as resources on the current gaps and areas of focus for research in the future.

A. Determination of Treatment Setting

Future research is needed to evaluate whether recently developed software to conduct the multidimensional assessment and yield an algorithmically derived placement recommendation leads to better outcomes than clinical judgment that may rely more generally on the six ASAM assessment dimensions and placement principles.

B. Pharmacotherapy

There are many unanswered questions regarding use of pharmacotherapy in SUD. The following are select examples of these questions. More research is needed to identify medications for the majority of the categories of SUD, including cannabis use disorder.

a. Opioid Use Disorder

While strong evidence supports opioid agonist therapy (OAT) and moderate evidence supports extended-release injectable naltrexone, some patients may prefer oral naltrexone despite its lack of demonstrated effectiveness. Further research is needed to determine whether additional measures to improve treatment retention and medication adherence (e.g., Contingency Management [CM]) would reduce opioid consumption in patients taking oral naltrexone.

Further research is needed to determine risks and benefits of buprenorphine/naloxone versus buprenorphine mono-product versus methadone for long-term outcome for children born to women with OUD.

b. Stimulant Use Disorder

Further research into the use of dexamphetamine to treat methamphetamine use disorder is indicated, as an initial study showed that its use increased participation in treatment while not decreasing use.[208] Given the potential misuse of dexamphetamine, the authors cannot recommend for its use without further evidence. A small RCT including only men who have sex with men with methamphetamine use disorder showed a benefit of the antidepressant mirtazapine compared to placebo in reducing methamphetamine use.[308] Further research is indicated into the use of mirtazapine to treat methamphetamine use disorder. Additional research should be conducted on pharmacotherapy for stimulant use disorders.

C. Psychosocial Interventions

a. Substance Use Disorders

Further research is needed regarding appropriate additional non-pharmacological therapy specific to the individual and to the setting of care. Additionally, research is needed regarding the comparative effectiveness of interventions when delivered to patients in groups. Current staffing models are based on care being delivered in a group format for all SUDs. More research is needed to determine specific protocols, efficacy and effectiveness of the group approach.

b. Opioid Use Disorder

Given patients' reluctance to accept referrals to SUD specialty care, clinical trials supporting delivery of AUD and OUD pharmacotherapy in general care settings using addiction-focused Medical Management offer promise of increasing rates of treatment for those with AUD and OUD. The provider time required by these protocols limits the generalizability of the findings based on current staffing models. Further research is needed to determine whether more cost-effective models could be developed for delivering addiction-focused Medical Management for OUD and AUD. For example, research is needed on the effectiveness of sharing various components of addiction-focused Medical Management effectively among members of a Patient-aligned Care Team and co-located Primary Care-Mental Health Integration therapists and prescribers, whether the initial session (40-60 minutes) could be shortened and whether telehealth could be utilized to deliver addiction-focused medical management. Further research is also needed to determine the benefits of additional psychosocial interventions to address co-occurring conditions in this setting versus referral to specialty SUD care.

D. Follow-up

Further research is needed to determine models for effective and cost-effective continuing care. While there is expert consensus based on observational studies that the benefits of engagement in continuing SUD care outweigh risks when patients relapse or continue to use substances, we have found no RCTs, automatic "disciplinary" discharge from treatment continues in practice. Further research may be needed to compare the risks and benefits of automatic discharge from care and of various models of adjusting care based on response to treatment.

E. Stabilization and Withdrawal

Further research is needed to define the risks and benefits of systematic assessment scales and decision support tools for withdrawal treatment in common treatment settings such as inpatient psychiatry units, residential SUD treatment programs and outpatient general mental health, general medicine, and specialty SUD treatment clinics.

F. Telehealth

Additional research on the use of telehealth in SUD may be beneficial, as evidence-based psychosocial interventions are not currently offered in all locations. Telehealth may help address barriers to care that contribute to low engagement in treatment in the SUD patient population.

Appendix A: Evidence Review Methodology

A. Developing the Scope and Key Questions

The CPG Champions, along with the Work Group, were tasked with identifying KQs to guide the SR of the literature on SUD. These questions, which were developed in consultation with the Lewin team, addressed clinical topics of the highest priority for the VA and DoD populations. The KQs follow the population, intervention, comparison, outcome, timing and setting (PICOTS) framework for evidence questions, as established by the Agency for Healthcare Research and Quality (AHRQ). Table A-1 provides a brief overview of the PICOTS typology.

Table A-1. PICOTS [309]

P	Patients, Population, or Problem	A description of the patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-occurring conditions, and other patient characteristics or demographics.
I	Intervention or Exposure	Refers to the specific treatments or approaches used with the patient or population. It includes doses, frequency, methods of administering treatments, etc.
C	Comparison	Describes the interventions or care that is being compared with the intervention(s) of interest described above. It includes alternatives such as placebo, drugs, surgery, lifestyle changes, standard of care, etc.
O	Outcome	Describes the specific results of interest. Outcomes can include short, intermediate, and long-term outcomes, or specific results such as quality of life, complications, mortality, morbidity, etc.
(T)	Timing, if applicable	Describes the duration of time that is of interest for the particular patient intervention and outcome, benefit, or harm to occur (or not occur).
(S)	Setting, if applicable	Describes the setting or context of interest. Setting can be a location (such as primary, specialty, or inpatient care).

The Champions and evidence review team carried out several iterations of this process, each time narrowing the scope of the CPG and the literature review by prioritizing the topics of interest. Due to resource constraints, all developed KQs were not able to be included in the systematic evidence review. Thus, the Champions and Work Group determined which questions were of highest priority, and those were included in the review. Table A-2 contains the final set of KQs used to guide the SR for this CPG.

a. Population(s)

The KQs are specific to adults 18 years or older who have a DSM diagnosis of SUD with or without other health conditions. The exception is KQ 4, which specifies patients who screened positive for unhealthy alcohol use based on Alcohol Use Disorders Identification Test- Consumption (AUDIT-C) criteria.

b. Interventions

Pharmacotherapies for AUD included: acamprosate, disulfiram, and naltrexone (either oral or depot extended-release injectable formulation). Off label medications for AUD were also considered. These included: aripiprazole, atomoxetine, baclofen, benzodiazepines, buspirone, citalopram, desipramine, fluoxetine, fluvoxamine, gabapentin, imipramine, olanzapine, ondansetron, paroxetine, quetiapine, sertraline, topiramate, valproic acid, and varenicline. For KQ 11, other anticonvulsants, gamma hydroxybutyrate, and clonidine were also considered. Pharmacotherapies for OUD included:

buprenorphine, buprenorphine/naloxone, methadone, oral naltrexone, and extended-release injectable naltrexone. For KQ 12, clonidine was also considered. Pharmacotherapies for cannabis use disorder included: bupropion, divalproex, gabapentin, nabilone, N-acetylcysteine, nefazodone, and dronabinol. Pharmacotherapies for cocaine/stimulant use disorder included: disulfiram, doxazosin, topiramate, modafinil, agonist replacement therapy, and baclofen.

A brief intervention (BI), which is defined as an intervention typically lasting from several minutes up to an entire visit and which is a patient-centered, empathetic brief counseling intervention that can be offered by a clinician who is not a specialist addictions provider or counselor, was also considered. A BI for unhealthy alcohol use is a single session or multiple sessions that include motivational discussion focused on increasing insight and awareness regarding alcohol use and motivation toward behavioral change. BIs can be tailored for variance in population or setting and can be used as a stand-alone treatment for those at-risk as well as a vehicle for engaging those in need of more extensive levels of care. Telephone or web-based BIs as sole treatment are beyond the scope of this guideline. However, their use as adjuncts to other treatment is within the scope of this guideline.

Criteria to determine initial treatment intensity and setting including disorder severity and psychosocial stability were included in the review.

Strategies for promoting active involvement in mutual help programs include branded 12-Step Facilitation (TSF) and other branded strategies (e.g., making Alcoholics Anonymous [AA] easier).

Psychotherapy and psychosocial interventions included: Behavioral Couples Counseling (BCC); Cognitive Behavioral Therapy (CBT); Community Reinforcement Approach (CRA); Contingency Management (CM)/motivational incentives; Motivational Enhancement Therapy (MET); twelve-step recovery; motivational interviewing (MI); individual social skills training; family psycho-education that aim to increase coping strategies, awareness, and self-monitoring behavior; and mindfulness (e.g., mindfulness-based recovery programs, meditation).

Possible components of addiction-focused Medical Management included: monitoring of self-reported use, laboratory markers, and consequences of substance use; monitoring of medication adherence, response to treatment, and adverse effects; integrated or non-integrated treatment of co-occurring mental health conditions; and education and referral to community support for recovery (e.g., AA). Possible components of measurement-based care included biomarkers and patient reports. Measurement instruments included the Brief Addiction Monitor (BAM) and measure of patient health (e.g., Patient Health Questionnaire [PHQ-9]).

c. Outcomes

Consumption outcomes included alcohol consumption (drinks per day), opioid consumption, return to any drinking, return to heavy drinking, drinking days, heavy drinking days (defined as four or more drinks per day for women and five or more drinks per day for men), drinks per drinking day, time to relapse, relapse, percent of heavy drinking days, adherence with treatment or abstinence, retention/engagement in the treatment program, number lost to treatment (stability and engagement), duration of involvement in treatment, adverse events, morbidity, mortality, overdoses, hospitalization or readmission, and emergency department utilization.

Side effects of medication included: withdrawals due to adverse events, nausea/vomiting, diarrhea, anorexia, palpitations, headache, dizziness, cognitive dysfunction, taste abnormalities, paresthesia (numbness, tingling), metabolic acidosis, glaucoma, vision changes, suicidal ideation, insomnia, anxiety, and rash.

Recovery outcomes included: days in the community, reduction in homelessness, decrease in encounters with criminal justice system, and increase in employment. Functional status and quality of life outcomes included: mental state, global functioning, social functioning, and quality of life and life satisfaction. Engagement outcomes included: minimum number of outpatient visits and minimal length of stay in an inpatient setting. Health outcomes included: accidents, injuries, mortality, healthcare utilization, functional status, and quality of life.

B. Conducting the Systematic Review

Extensive literature searches using the search terms and strategy included in Appendix H identified 4,708 citations potentially addressing the KQs of interest to this evidence review. Of those, 2,100 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date, not a full-length article). Overall, 2,608 abstracts were reviewed with 1,621 of those being excluded for the following reasons: not a SR or clinical study, did not address a KQ of interest to this review, did not enroll a population of interest, or published prior to November 2007. A total of 987 full-length articles were reviewed. Of those, 682 were excluded at a first pass review for the following: not addressing a KQ of interest, not enrolling the population of interest, not meeting inclusion criteria for clinical study or SR, not meeting inclusion criteria for any KQ, or being a duplicate. A total of 305 full-length articles were thought to address one or more KQs and were further reviewed. Of these, 184 were ultimately excluded. Reasons for their exclusion are presented in Figure A-1 below.

Overall, 135 studies (in 136 articles) addressed one or more of the KQs and were considered as evidence in this review. Table A-2 indicates the number of studies that addressed each of the questions.

Figure A-1. Study Flow Diagram

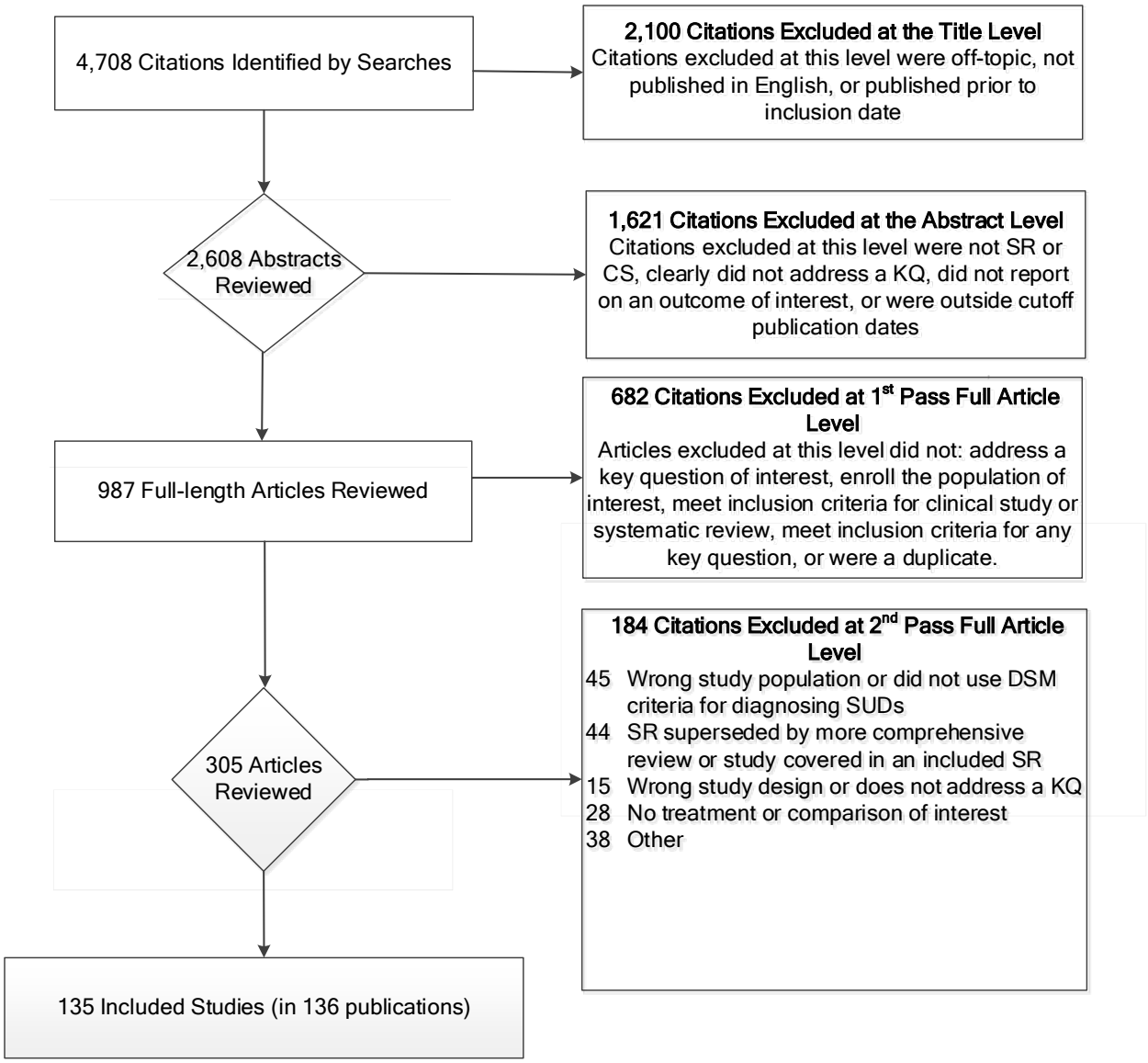


Table A-2. Evidence Base for Key Questions

Question Number	Question	Number of Studies and Type of Studies	Relevant Recommendations
1	In adults with a DSM diagnosis of AUD, what is the comparative effectiveness of different medications for improving consumption outcomes, adherence outcomes, and adverse events in the following? a) Primary care b) Specialty care	3 SRs and 6 RCTs	5,6
2	In adults with a DSM diagnosis of OUD what is the comparative effectiveness of different management approaches, including different intensity and lengths of stay in treatment, for improving consumption outcomes, adherence outcomes, and adverse events in the following? a) Primary care b) Specialty care	3 SRs and 8 RCTs	8, 9, 10, 11, 12, 33
3	In adults with a DSM diagnosis of OUD in the primary care setting, what is the comparative effectiveness of pharmacologic-assisted therapy with or without non-pharmacologic therapy for improving consumption outcomes, adherence outcomes, and adverse events?	2 SRs and 2 RCTs	13
4	In adults who screened positive using the AUDIT-C for unhealthy alcohol use, what is the comparative effectiveness of the following for improving consumption and health outcomes? a) Components of brief interventions b) Single compared to multiple brief interventions	4 SRs and 17 RCTs	2
5	In adults with a DSM diagnosis of AUD, what criteria can be used to determine the appropriate initial intensity and setting of specialty substance use care for improving consumption, health, and engagement outcomes?	No studies identified by our searches	4
6	In adults with a DSM diagnosis of an SUD, what is the comparative effectiveness of strategies used for promoting active involvement in available mutual help programs (e.g., TSF) for improving consumption, health, and engagement outcomes?	2 SRs and 8 RCTs	21
7a AUD	In adults with a DSM diagnosis of an SUD, what is the comparative effectiveness of addiction-focused psychotherapies or psychosocial interventions for improving consumption outcomes, adherence outcomes, and recovery outcomes?	4 SRs and 13 RCTs	7
7b OUD		7 RCTs	14, 15, 16
7c cannabis use disorder		2 SRs and 3 RCTs	18
7d cocaine/ stimulant use disorder		2 SRs and 14 RCTs	20
8	In adults with a DSM diagnosis of an SUD, what is the comparative effectiveness of the following aspects of measurement-based care in primary care and specialty care settings for improving consumption and health outcomes? a) Components of measurement-based care b) Frequency of measurement	2 RCTs	23

Question Number	Question	Number of Studies and Type of Studies	Relevant Recommendations
9	In adults with a DSM diagnosis of a cannabis use disorder, what is the comparative effectiveness of different management approaches for improving consumption outcomes, adherence outcomes, and adverse events in the following? a) Primary or general mental health care b) Specialty SUD care	5 RCTs	17
10	In adults with a DSM diagnosis of stimulant/cocaine use disorder, what is the comparative effectiveness of disulfiram, topiramate and other off-label medications for improving consumption outcomes, adherence outcomes, and adverse events?	2 SRs and 14 RCTs	19
11	For patients with moderate to severe risk of alcohol withdrawal, what is the comparative effectiveness of medication for stabilization?	2 SRs and 6 RCTs	27, 28, 30, 31
12	For patients with moderate to severe risk of opioid withdrawal, what is the comparative effectiveness of medication for stabilization? Does comparative effectiveness vary based on dosing and time course used with these medications?	3 SRs and 3 RCTs	34, 35
Total Evidence Base		**135 studies**	

Abbreviations: AUD: alcohol use disorder; DSM: Diagnostic and Statistical Manual of Mental Disorders; OUD: opioid use disorder; RCT: randomized controlled trial; SR: systematic review; SUD: substance use disorders; TSF: 12-Step Facilitation

a. Criteria for Study Inclusion/Exclusion

i. General Criteria

- Clinical studies or SRs published on or after November 1, 2007
- Studies must be published in English
- Publication must be a full clinical study or SR; abstracts alone were not included. Similarly, letters, editorials, and other publications that are not full-length, clinical studies were not accepted as evidence.
- Studies enrolled adults 18 years or older. In studies that mixed adults and children, at least 80% of the enrolled patients had to be 18 years or older.
- Studies must have enrolled a patient population where at least 80% of patients met the required diagnostic criteria.
- Studies of intervention outcomes must have followed patients for at least 12 weeks post-randomization unless otherwise noted (KQ 5, 6, 11, and 12 are exempt from this requirement).
- Studies that specifically focus on incarcerated substance use offenders or driving while intoxicated/driving under the influence offenders were excluded.

ii. Pharmacotherapy/Non-pharmacologic Therapy for SUD (KQ 1-4, 6-10)

- Studies must have been RCTs or SRs of RCTs. In the absence of such evidence, prospective comparative studies will be reviewed.
- Randomized crossover trials were considered only if data from the first treatment period were reported separately.
- Studies must have enrolled ≥10 patients per treatment arm.

iii. Criteria for Determining Appropriate Initial Intensity and Setting of Specialty Substance Use Care (KQ 5)

- Studies must have compared different criteria and enrolled ≥ 10 patients per treatment arm.

b. Literature Search Strategy

Information regarding the bibliographic databases, date limits, and platform/provider can be found in Table A-3, below. Additional information on the search strategies, including topic-specific search terms and search strategies can be found in Appendix H.

Table A-3. Bibliographic Database Information

Name	Date Limits	Platform/Provider
Bibliographic Databases		
The Cochrane Central Register of Controlled Trials (CENTRAL)	2007 through January 2015	Wiley
The Cochrane Database of Methodology Reviews (Methodology Reviews)	2007 through January 2015	Wiley
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	2007 through January 2015	Wiley
Database of Abstracts of Reviews of Effects	2007 through January 2015	Wiley
EMBASE (Excerpta Medica)	2007 through January 2015	Elsevier
Health Technology Assessment Database (HTA)	2007 through January 2015	Wiley
MEDLINE/PreMEDLINE	2007 through January 2015	OVIDSP
PsycINFO	2007 through January 2015	OVIDSP
PubMed (In-process and Publisher records)	2007 through January 2015	NLM
Gray Literature Resources		
AHRQ	2007 through January 2015	AHRQ
Healthcare Standards database	2007 through January 2015	ECRI Institute
National Guideline Clearinghouse™	2007 through January 2015	AHRQ
National Institute of Health and Clinical Excellence	2007 through January 2015	NHS
TRIP database	2007 through January 2015	TRIP

C. Convening the Face-to-face Meeting

In consultation with the contracting officer's representative (COR), the Champions, and the Work Group, the Lewin Team convened a three and a half day face-to-face meeting of the CPG Champions and Work Group members on April 14-17, 2015. These experts were gathered to develop and draft the clinical

recommendations for an update to the 2009 SUD CPG. Lewin presented findings from the evidence review of KQs 1-10 in order to facilitate and inform the process.

Under the direction of the Champions, the Work Group members were charged with interpreting the results of the evidence review, and asked to categorize and carry forward recommendations from the 2009 SUD CPG, modifying the recommendations as necessary. The members also developed new clinical practice recommendations not presented in the 2009 SUD CPG, based on the 2015 evidence review. The subject matter experts were divided into three smaller subgroups at this meeting.

As the Work Group members drafted clinical practice recommendations, they also assigned a grade for each recommendation based on a modified GRADE and USPSTF methodology. Each recommendation was graded by assessing the quality of the overall evidence base, the associated benefits and harms, the variation in values and preferences, and other implications of the recommendation.

In addition to developing recommendations during the face-to-face meeting, the Work Group members also revised the 2009 SUD CPG algorithms to reflect the new and amended recommendations. They discussed the available evidence as well as changes in clinical practice since 2009, as necessary, to update the algorithms.

KQs 11 and 12 were developed following the face-to-face meeting, after the need to systematically review the evidence related to stabilization for withdrawal from alcohol and opioids was identified. For KQs 11 and 12, the process for developing and categorizing recommendations was adapted to be used in a teleconference format following the face-to-face meeting.

D. Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a grade for the strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation:[34]

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Values and preferences
- Other implications, as appropriate, e.g.,:
    - Resource Use
    - Equity
    - Acceptability
    - Feasibility
    - Subgroup considerations

The following sections further describe each domain.

Balance of desirable and undesirable outcomes refers to the size of anticipated benefits (e.g., increased longevity, reduction in morbid event, resolution of symptoms, improved quality of life (QoL), decreased

resource use) and harms (e.g., decreased longevity, immediate serious complications, adverse event, impaired quality of life, increased resource use, inconvenience/hassle) relative to each other. This domain is based on the understanding that the majority of clinicians will offer patients therapeutic or preventive measures as long as the advantages of the intervention exceed the risks and adverse effects. The certainty or uncertainty of the clinician about the risk-benefit balance will greatly influence the strength of the recommendation.

Some of the discussion questions that fall under this domain include:

- Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?
- Are the desirable anticipated effects large?
- Are the undesirable anticipated effects small?
- Are the desirable effects large relative to undesirable effects?

Confidence in the quality of the evidence reflects the quality of the evidence base and the certainty in that evidence. This second domain reflects the methodological quality of the studies for each outcome variable. In general, the strength of recommendation follows the level of evidence, but not always, as other domains may increase or decrease the strength. The evidence review used for the development of recommendations for SUD, conducted by ECRI, assessed the confidence in the quality of the evidence base and assigned a rate of "High," "Moderate," "Low," or "Very Low."

The elements that go into the confidence in the quality of the evidence include:

- Is there high or moderate quality evidence that answers this question?
- What is the overall certainty of this evidence?

Values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life. More precisely, it refers to the processes that individuals use in considering the potential benefits, harms, costs, limitations, and inconvenience of the therapeutic or preventive measures in relation to one another. For some, the term "values" has the closest connotation to these processes. For others, the connotation of "preferences" best captures the notion of choice. In general, values and preferences increase the strength of the recommendation when there is high concordance and decrease it when there is great variability. In a situation in which the balance of benefits and risks are uncertain, eliciting the values and preferences of patients and empowering them and their surrogates to make decisions consistent with their goals of care becomes even more important. A recommendation can be described as having "similar values," "some variation," or "large variation" in typical values and preferences between patients and the larger populations of interest.

Some of the discussion questions that fall under the purview of values and preferences include:

- Are you confident about the typical values and preferences and are they similar across the target population?
- What are the patient's values and preferences?
- Are the assumed or identified relative values similar across the target population?

Other implications consider the practicality of the recommendation, including resources use, equity, acceptability, feasibility and subgroup considerations. Resource use is related to the uncertainty around the cost-effectiveness of a therapeutic or preventive measure. For example statin use in the frail elderly and others with multiple co-occurring conditions may not be effective and depending on the societal benchmark for willingness to pay, may not be a good use of resources. Equity, acceptability, feasibility, and subgroup considerations require similar judgments around the practically of the recommendation.

The framework below was used by the Work Group to guide discussions on each domain.

Table A-3. Evidence to Recommendation Framework

Decision Domain	Judgment
Balance of desirable and undesirable outcomes	
▪ Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa? ▪ Are the desirable anticipated effects large? ▪ Are the undesirable anticipated effects small? ▪ Are the desirable effects large relative to undesirable effects?	Benefits outweigh harms/burden Benefits slightly outweigh harms/burden Benefits and harms/burden are balanced Harms/burden slightly outweigh benefits Harms/burden outweigh benefits
Confidence in the quality of the evidence	
▪ Is there high or moderate quality evidence that answers this question? ▪ What is the overall certainty of this evidence?	High Moderate Low Very low
Values and preferences	
▪ Are you confident about the typical values and preferences and are they similar across the target population? ▪ What are the patient's values and preferences? ▪ Are the assumed or identified relative values similar across the target population?	Similar values Some variation Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	
▪ Are the resources worth the expected net benefit from the recommendation? ▪ What are the costs per resource unit? ▪ Is this intervention generally available? ▪ Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? ▪ Is there lots of variability in resource requirements across settings?	Various considerations

The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which combines the four domains.[34] GRADE methodology does not allow for recommendations to be made based on expert opinion alone. While strong recommendations are usually based on high or moderate confidence in the estimates of effect (quality of the evidence) there may be instances where strong recommendations are warranted even when the quality of evidence is low.[310] In these types of instances where the balance of desirable and undesirable outcomes and values and preferences played

large roles in determining the strength of a recommendation, this is explained in the discussion section for the recommendation.

The GRADE of a recommendation is based on the following elements:

- Four decision domains used to determine the strength and direction (described above)
- Relative strength (Strong or Weak)
- Direction (For or Against)

The relative strength of the recommendation is based on a binary scale, "Strong" or "Weak." A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong For (or "We recommend offering this option …")
- Weak For (or "We suggest offering this option …")
- Weak Against (or "We suggest not offering this option …")
- Strong Against (or "We recommend against offering this option …")

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified." Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

E. Recommendation Categorization

a. Recommendation Categories and Definitions

For use in the 2015 SUD CPG, a set of recommendation categories was adapted from those used by the United Kingdom National Institute for Health and Clinical Excellence (NICE). [37,38] These categories, along with their corresponding definitions, were used to account for the various ways in which recommendations could have been updated from the 2009 SUD CPG. The categories and definitions can be found in Table A-4.

Table A-4. Recommendation Categories and Definitions

Evidence Reviewed*	Recommendation Category*	Definition*
Reviewed	New-added	New recommendation following review of the evidence
	New-replaced	Recommendation from previous CPG that has been carried over to the updated CPG that has been changed following review of the evidence
	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed but the recommendation is not changed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed based on review of the evidence
Not reviewed	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG, but for which the evidence has not been reviewed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has not been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed because it was deemed out of scope for the updated CPG

*Adapted from the NICE guideline manual (2012) [37] and Garcia et al. (2014) [38]
Abbreviation: CPG: clinical practice guideline

b. Categorizing Recommendations with an Updated Review of the Evidence

Recommendations were first categorized by whether or not they were based on an updated review of the evidence. If evidence had been reviewed, recommendations were categorized as "New-added," "New-replaced," "Not changed," "Amended," or "Deleted."

"Reviewed, New-added" recommendations were original, new recommendations that were not in the 2009 SUD CPG. "Reviewed, New-replaced" recommendations were in the previous version of the guideline, but were modified to align with the updated review of the evidence. These recommendations could have also included clinically significant changes to the previous version. Recommendations categorized as "Reviewed, Not changed" were carried forward from the previous version of the CPG unchanged.

To maintain consistency between 2009 recommendations, which were developed using the USPSTF methodology, and 2015 recommendations, which were developed using the GRADE methodology, it was necessary to modify the 2009 recommendations to include verbiage to signify the strength of the recommendation (e.g., "We recommend," "We suggest"). Because the 2009 recommendations inherently needed to be modified at least slightly to include this language, the "Not changed" category was not used. For recommendations carried forward to the updated CPG with review of the evidence and slightly modified wording, the "Reviewed, Amended" recommendation category was used. This allowed for the wording of the recommendation to reflect GRADE methodology as well as for any other non-substantive (i.e., not clinically meaningful) language changes deemed necessary. The evidence used to support these

recommendations was carried forward from the previous version of the CPG and/or was identified in the evidence review for the update.

Recommendations could have also been designated "Reviewed, Deleted." These were recommendations from the previous version of the CPG that were not brought forward to the updated guideline after review of the evidence. This occurred if the evidence supporting the recommendations was out of date, to the extent that there was no longer any basis to recommend a particular course of care and/or new evidence suggests a shift in care, rendering recommendations in the previous version of the guideline obsolete.

c. Categorizing Recommendations without an Updated Review of the Evidence

There were also cases in which it was necessary to carry forward recommendations from the previous version of the CPG without a SR of the evidence. Due to time and budget constraints, the update of the SUD CPG could not review all available evidence on management of SUD, but instead focused its KQs on areas of new or updated scientific research or areas that were not previously covered in the CPG.

For areas of research that have not changed, and for which recommendations made in the previous version of the guideline were still relevant, recommendations could have been carried forward to the updated guideline without an updated SR of the evidence. The support for these recommendations in the updated CPG was thus also carried forward from the previous version of the CPG. These recommendations were categorized as "Not reviewed." If evidence had not been reviewed, recommendations could have been categorized as "Not changed," Amended," or "Deleted."

"Not reviewed, Not changed" recommendations refer to recommendations from the previous version of the SUD CPG that were carried forward unchanged to the updated version. The category of "Not reviewed, Amended" was used to designate recommendations which were modified from the 2009 CPG with the updated GRADE language, as explained above.

Recommendations could also have been categorized as "Not reviewed, Deleted" if they were determined to be out of scope. A recommendation was out of scope if it pertained to a topic (e.g., population, care setting, treatment, condition) outside of the scope for the updated CPG as defined by the Work Group.

The categories for the recommendations included in the 2015 version of the guideline are noted in the Recommendations. Recommendations 1, 22, 24, 25, 26, 29, and 32 were carried forward from the 2009 SUD CPG using this method. The categories for the recommendations from the 2009 SUD CPG are noted in Appendix E.

F. Drafting and Submitting the Final Clinical Practice Guideline

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments to craft discussion sections to support each of the new recommendations and/or to update discussion sections from the 2009 SUD CPG to support the amended "carried forward" recommendations. The Work Group also considered tables, appendices, and other sections from the 2009 SUD CPG for inclusion in the update. During this time, the Champions and Work Group also made additional revisions to the algorithms, as necessary.

After developing the initial draft of the updated CPG, an iterative review process was used to solicit feedback on and make revisions to the CPG. Once they were developed, the first two drafts of the CPG were posted on a wiki website for a period of 14-20 business days for internal review and comment by the Work Group. All feedback submitted during each review period was reviewed and discussed by the Work Group and appropriate revisions were made to the CPG.

Draft 3 of the CPG was made available for peer review and comment. This process is described in Peer Review Process. After revisions were made based on the feedback received during the peer review and comment period, the Champions presented the CPG to the EBPWG for their approval. Changes were made based on feedback from the EBPWG and the guideline was finalized.

The Work Group also produced a set of guideline toolkit materials which included a provider summary, pocket cards, and a patient summary. The final 2015 SUD CPG was submitted to the EBPWG in December 2015.

Appendix B: Pharmacotherapy for Alcohol Use Disorder and Opioid Use Disorder

Table B-1. Pharmacotherapy for Alcohol Use Disorder

Naltrexone Oral	Naltrexone Injectable	Acamprosate	Disulfiram	Topiramate[1]	Gabapentin[1]
Indications					
AUD (DSM diagnosis) with: 1. At least 3-5 days of pretreatment abstinence not required but may improve response 2. Initial engagement in addiction-focused Medial Management and/or other recommended psychosocial intervention	AUD (DSM diagnosis) with: 1. Pretreatment abstinence not required but may improve response 2. Willingness to receive monthly injections 3. Difficulty adhering to an oral regimen 4. Initial engagement in addiction-focused Medial Management and/or other recommended psychosocial intervention	AUD (DSM diagnosis) with: 1. Abstinence at treatment initiation 2. Initial engagement in addiction-focused Medial Management and/or other recommended psychosocial intervention	AUD (DSM diagnosis) with: 1. Abstinence >12 hours and BAL=0 2. Combined cocaine dependence 3. Previous response to disulfiram 4. Capacity to appreciate risks and benefits and to consent to treatment 5. Initial engagement in addiction-focused Medial Management and/or other recommended psychosocial intervention 6. Note: More effective with monitored administration (e.g., in clinic, with spouse, with probation officer)	AUD (DSM diagnosis) (off label) with: 1. Pretreatment abstinence not required but may improve response 2. Initial engagement in addiction-focused Medial Management and/or other recommended psychosocial intervention	AUD (DSM diagnosis) (off label) with: 1. Pretreatment abstinence not required but may improve response 2. Initial engagement in addiction-focused Medial Management and/or other recommended psychosocial intervention

[1] Not FDA labeled for treatment of AUD

Naltrexone Oral	Naltrexone Injectable	Acamprosate	Disulfiram	Topiramate[1]	Gabapentin[1]
Contraindications					
■ Receiving opioid agonists ■ Physiologic opioid dependence with use within past 7 days ■ Acute opioid withdrawal ■ Failed naloxone challenge test ■ Positive urine opioid screen ■ Acute hepatitis or liver failure ■ Hypersensitivity	■ Receiving opioid agonists ■ Physiologic opioid dependence with use within past 7 days ■ Acute opioid withdrawal ■ Failed naloxone challenge test ■ Positive urine opioid screen ■ Acute hepatitis or liver failure ■ Hypersensitivity ■ Inadequate muscle mass	■ Hypersensitivity ■ Severe renal insufficiency (CrCl ≤30 mL/min)	■ Severe cardiovascular, respiratory, or renal disease ■ Severe hepatic dysfunction (i.e., transaminase levels >3 times upper limit of normal or abnormal bilirubin) ■ Severe psychiatric disorders, especially psychotic and cognitive disorders and suicidal ideation ■ Poor impulse control ■ Metronidazole or ketoconazole therapy which already induce a similar reaction to alcohol ■ Hypersensitivity	■ No contraindications in manufacturer's labeling	■ Hypersensitivity

Naltrexone Oral	Naltrexone Injectable	Acamprosate	Disulfiram	Topiramate[1]	Gabapentin[1]
Warnings/Precautions					
▪ Active liver disease ▪ Severe renal failure ▪ Pregnancy Category C	▪ Active liver disease ▪ Uncertain effects (no data) in moderate to severe renal insufficiency ▪ Injection site reactions ▪ Use intramuscular injections with caution in patients with thrombocyto-penia or coagulation disorders ▪ Pregnancy Category C	▪ Monitor for emergence of depression or suicidality ▪ Reduce dose in patients with renal insufficiency, including elderly ▪ Pregnancy Category C	▪ Alcohol-disulfiram reaction; patients must be vigilant to avoid alcohol in all forms including mouthwash, over the counter medications, etc. ▪ Pregnancy Category C	▪ Do not abruptly discontinue therapy; taper dosage gradually ▪ Cognitive dysfunction, psychiatric disturbances, and sedation may occur with use ▪ Increased risk of suicidal ideation with antiepileptic agents, including topiramate ▪ Pregnancy Category C	▪ Do not abruptly discontinue therapy; taper dosage gradually ▪ May cause CNS depression including somnolence/ dizziness ▪ Increased risk of suicidal ideation with antiepileptic agents, including gabapentin ▪ Pregnancy Category C
Baseline Evaluation					
▪ Liver transaminase levels ▪ Bilirubin within normal limits ▪ Urine beta-HCG for females	▪ Liver transaminase levels ▪ Bilirubin within normal limits ▪ CrCl (estimated or measured) 50 mL/min or greater ▪ Ensure patient has adequate muscle mass for injection ▪ Urine beta-HCG for females	▪ CrCl (estimated or measured) ▪ Urine beta-HCG for females	▪ Liver transaminase levels ▪ Physical assessment ▪ Psychiatric assessment ▪ Electrocardiogram if indicated by history of cardiac disease ▪ Verify abstinence with breath or BAL ▪ Urine beta-HCG for females	▪ Assess renal function ▪ Urine beta-HCG for females	▪ Assess renal function ▪ Urine beta-HCG for females

Naltrexone Oral	Naltrexone Injectable	Acamprosate	Disulfiram	Topiramate[1]	Gabapentin[1]
Dosage and Administration					
▪ 50-100 mg orally 1 time daily	▪ 380 mg 1 time monthly by deep intramuscular injection	▪ 666 mg orally 3 times daily, preferably with meals	▪ 250 mg orally 1 time daily (range, 125-500 mg daily)	▪ Titrate up gradually over several weeks to minimize side effects ▪ Initiate at 50 mg/day; increase to a maximum dose of 100 mg 2 times daily	▪ Titrate up gradually to minimize side effects ▪ Initiate at 300 mg on day 1 and increase by 300 mg daily as tolerated to target of 1800 mg daily, administered in 3 divided doses
Alternative Dosing Schedules					
▪ 25 mg 1- or 2-time(s) daily with meals to reduce nausea, especially during the first week ▪ 100 mg on Monday and Wednesday and 150 mg on Friday			▪ Reduce dose to 125 mg to reduce side effects ▪ For monitored administration, consider giving 500 mg on Monday, Wednesday, and Friday	▪ Geriatric patients with CrCl <70 mL/min/1.73m^2 give initial dose of 25 mg/day followed by incremental increases of 25 mg at weekly intervals until an effective dose is reached	
Dosing in Special Populations					
▪ Hepatic or renal insufficiency: Use caution	▪ Mild renal insufficiency (CrCl 50-80 mL/min): No dosage adjustment necessary ▪ Uncertain effects (no data) in moderate to severe renal insufficiency	▪ Moderate renal insufficiency (CrCl 30-50 mL/min): 333 mg 3 times daily ▪ Do not administer to patients with severe renal insufficiency (CrCl ≤30 mL/min)		▪ CrCl <70 mL/minute/1.73m^2: Administer 50% dose and titrate more slowly ▪ Dosage adjustment may be required in hepatic impairment	▪ Dosage must be adjusted for renal function, consider target dose <1800 mg daily when CrCl <60 mL/min

Naltrexone Oral	Naltrexone Injectable	Acamprosate	Disulfiram	Topiramate[1]	Gabapentin[1]
Adverse Effects					
▪ Common: Nausea ▪ Other: Headache, dizziness, nervousness, fatigue, insomnia, vomiting, anxiety, somnolence	▪ Major: Eosinophilic pneumonia, depression, suicidality ▪ Common: Injection-site reactions, injection site tenderness, injection site induration, nausea, headache, asthenia	▪ Major: Suicidality 2.4% (vs. 0.8% on placebo during the first year in clinical trials) ▪ Common: Diarrhea (16%) ▪ Other: Anxiety, asthenia, depression, insomnia	▪ Major: Hepatotoxicity, peripheral neuropathy, psychosis, delirium, severe disulfiram-ethanol reaction ▪ Common: Somnolence, metallic taste, headache	▪ CNS: Paresthesia, nervousness, fatigue, ataxia, drowsiness, lack of concentration, memory impairment, confusion ▪ Gastrointestinal: Abdominal pain, anorexia	▪ CNS: Dizziness, drowsiness, ataxia, fatigue ▪ Gastrointestinal: Diarrhea, nausea/vomiting, abdominal pain
Drug Interactions					
▪ Opioid-containing medications, including over the counter preparations ▪ Thioridazine (increased lethargy and somnolence)	▪ Opioid-containing medications, including over the counter preparations ▪ Thioridazine (increased lethargy and somnolence)	▪ Naltrexone: 33% increase in Cmax of acamprosate (no dosage adjustment is recommended) ▪ Antidepressants: Weight gain and weight loss more common than with either medication alone	▪ Alcohol containing medications, including over the counter preparations ▪ Drug-drug interactions may occur with phenytoin, warfarin, isoniazid, rifampin, diazepam, chlordiazepoxide, imipramine, desipramine, and oral hypoglycemic agents	▪ Use extreme caution if used concurrently with alcohol or other CNS depressants ▪ Topiramate may decrease the serum concentrations of contraceptives and decrease their effectiveness	▪ Use extreme caution if used concurrently with alcohol or other CNS depressants ▪ Antacids may decrease levels of gabapentin

Naltrexone Oral	Naltrexone Injectable	Acamprosate	Disulfiram	Topiramate[1]	Gabapentin[1]
Monitoring					
▪ Repeat liver transaminase levels at 6 and 12 months and then every 12 months thereafter ▪ Discontinue medication and consider alternatives if no detectable benefit after an adequate trial (50 mg daily for 3 months)	▪ Repeat liver transaminase levels at 6 and 12 months and then every 12 months thereafter ▪ Discontinue if there is no detectable benefit within 3 months	▪ Monitor serum creatinine/CrCl, particularly in the elderly and in patients with renal insufficiency ▪ Maintain therapy if relapse occurs	▪ Repeat liver transaminase levels within the first month, then monthly for first 3 months, and periodically thereafter as indicated ▪ Consider discontinuation in event of relapse or when patient is not available for supervision and counseling	▪ Monitor serum creatinine/CrCl periodically, particularly in patients with renal insufficiency and in geriatric patients ▪ Monitor for change in behavior which might indicate suicidal thoughts or depression ▪ Discontinue medication and consider alternatives if no detectable benefit after an adequate trial (300 mg daily for 3 months)	▪ Monitor serum creatinine/CrCl periodically, particularly in patients with renal insufficiency and in geriatric patients ▪ Monitor for change in behavior which might indicate suicidal thoughts or depression ▪ Gabapentin has abuse potential when taken in supratherapeutic dosages; monitor quantities prescribed and usage patterns ▪ Discontinue medication and consider alternatives if no detectable benefit from at least 900 mg daily for 2-3 months

<table>
<tr><th>Naltrexone Oral</th><th>Naltrexone Injectable</th><th>Acamprosate</th><th>Disulfiram</th><th>Topiramate[1]</th><th>Gabapentin[1]</th></tr>
<tr><td colspan="6">Patient Education</td></tr>
<tr><td>■ Discuss compliance enhancing methods
■ Negotiate commitment from the patient regarding monitored ingestion
■ Side effects, if any, tend to occur early in treatment and can typically resolve within 1-2 weeks after dosage adjustment</td><td>■ Report any concerning injection site reactions
■ Report any new or worsening depression or suicidal thinking
■ May cause allergic pneumonia; contact provider if patient develops signs and symptoms of pneumonia</td><td rowspan="2">■ Report any new or worsening depression or suicidal thinking</td><td rowspan="2">■ Avoid alcohol in food and beverages, including medications
■ Avoid disulfiram if alcohol intoxicated
■ May cause sedation; caution operating vehicles and hazardous machinery
■ Discuss compliance enhancing methods
■ Family members should not administer disulfiram without informing patient
■ Provide patients with wallet cards that indicate the use of disulfiram</td><td rowspan="2">■ Administer without regard to meals
■ It is not recommended to crush, break, or chew immediate release tablets due to bitter taste
■ Caution patients about performing tasks requiring mental alertness</td><td rowspan="2">■ Take first dose on first day at bedtime to minimize somnolence and dizziness
■ Caution patients about performing tasks requiring mental alertness</td></tr>
<tr><td colspan="2">■ If signs and symptoms of acute hepatitis occur, discontinue naltrexone and contact provider immediately
■ Very large doses of opioids may overcome the effects of naltrexone and lead to serious injury, coma, or death
■ Small doses of opioids, such as in analgesic, antidiarrheal, or antitussive drugs, may be blocked by naltrexone and fail to produce a therapeutic effect
■ Patients who have previously used opioids may be more sensitive to toxic effects of opioids after discontinuation of naltrexone</td></tr>
</table>

Abbreviations: AUD: alcohol use disorder; BAL: blood alcohol level; Cmax: maximum concentration; CNS: central nervous system; CrCl: creatinine clearance; DSM: Diagnostic and Statistical Manual of Mental Disorders; HCG: human chorionic gonadotropin; m: meter(s); mg: milligram(s); min: minute(s); mL: milliliter(s)

Table B-2. Pharmacotherapy for Opioid Use Disorder

Methadone	Buprenorphine/Naloxone or Buprenorphine	Naltrexone Injectable
Indications		
▪ OUD (DSM diagnosis) and patient meets Federal OTP Standards (42 C.F.R. §8.12)	▪ OUD (DSM diagnosis)	▪ OUD (DSM diagnosis) with: 1. Pretreatment abstinence from opioids and no signs of opioid withdrawal 2. Willingness to receive monthly injections
Contraindications		
▪ Hypersensitivity	▪ Hypersensitivity	▪ Receiving opioid agonists ▪ Physiologic opioid dependence with use within past 7 days ▪ Acute opioid withdrawal ▪ Failed naloxone challenge test ▪ Positive urine opioid screen ▪ Acute hepatitis or liver failure ▪ Hypersensitivity ▪ Inadequate muscle mass
Warnings/Precautions		
▪ Concurrent enrollment in another OTP ▪ Prolonged QTc interval ▪ Use caution in patients with respiratory, liver, or renal insufficiency ▪ Concurrent benzodiazepines or other CNS depressants including active AUD (potential respiratory depression) and other opioid agonists (check PDMP) ▪ Use of opioid antagonists (e.g., parenteral naloxone, oral or parenteral nalmefene, naltrexone)	▪ Buprenorphine/naloxone may precipitate withdrawal in patients on full agonist opioids ▪ Use caution in patients with respiratory, liver, or renal insufficiency ▪ Concurrent benzodiazepines or other CNS depressants, including active AUD (potential respiratory depression) ▪ Use of opioid antagonists (e.g., parenteral naloxone, oral or parenteral nalmefene, naltrexone)	▪ Active liver disease ▪ Uncertain effects (no data) in moderate to severe renal insufficiency ▪ Injection site reactions ▪ Use intramuscular injections with caution in patients with thrombocytopenia or coagulation disorders ▪ Pregnancy Category C
Baseline Evaluation		
▪ Consider baseline electrocardiogram and physical examination for patients at risk for QT prolongation or arrhythmias	▪ Liver transaminases	▪ Liver transaminase levels ▪ Bilirubin within normal limits ▪ CrCl (estimated or measured) 50 mL/min or greater ▪ Ensure patient has adequate muscle mass for injection ▪ Urine beta-HCG for females

Methadone	Buprenorphine/Naloxone or Buprenorphine	Naltrexone Injectable
Dosage and Administration		
▪ Initial dose: 15-20 mg single dose, maximum 30 mg ▪ Daily dose: Maximum 40 mg/day on first day ▪ Usual dosage range for optimal effects: 60-120 mg/day ▪ Titrate carefully, consider methadone's delayed cumulative effects ▪ Give orally in single dose ▪ Individualize dosing regimens (avoid same fixed dose for all patients)	Sublingual dosing: ▪ Induction dose: 2-8 mg 1 time daily ▪ Day 2 and onward: Increase dose by 2-4 mg/day until withdrawal symptoms and craving are relieved ▪ Stabilization/maintenance: Titrate by 2-4 mg/day targeting craving and illicit opioid use; usual dose 12-16 mg/day (up to 32 mg/day) ▪ Individualize dosing regimens ▪ For any formulation: Do not chew, swallow, or move after placement	▪ 380 mg 1 time monthly by deep intramuscular injection
Alternative Dosing Schedules		
▪ Give in divided daily doses based on peak and low levels that document rapid metabolism that justifies divided doses	▪ Give equivalent weekly maintenance dose divided over extended dosing intervals (2 or 3 times weekly or every 2, 3, or 4 days)	
Dosing in Special Populations		
▪ Renal or hepatic impairment: Reduce dose ▪ Elderly or debilitated: Reduce dose	▪ Hepatic impairment: Reduce dose ▪ For concurrent chronic pain, consider dividing total daily dose into 2- or 3-time daily administration	▪ Mild renal insufficiency (CrCl 50-80 mL/min): No dosage adjustment necessary ▪ Uncertain effects (no data) in moderate to severe renal insufficiency
Adverse Effects		
▪ Major: Respiratory depression, shock, cardiac arrest, prolongation of QTc interval on electrocardiogram and torsades de pointes ventricular tachycardia ▪ Common: Lightheadedness, dizziness, sedation, nausea, vomiting, sweating, constipation, edema ▪ Less common: Sexual dysfunction	▪ Major: Hepatitis, hepatic failure, respiratory depression (usually when misused intravenously or if combined with other CNS depressants) ▪ Common: Headache, pain, abdominal pain, insomnia, nausea, vomiting, sweating, constipation ▪ Sublingual buprenorphine/naloxone: Oral hypoesthesia, glossodynia, oral mucosal erythema	▪ Major: Eosinophilic pneumonia, depression, suicidality ▪ Common: Injection-site reaction, injection site tenderness, injection site induration, nausea, headache, asthenia

Methadone	Buprenorphine/Naloxone or Buprenorphine	Naltrexone Injectable
Drug Interactions		
▪ Drugs that reduce serum methadone levels: Ascorbic acid, barbiturates, carbamazepine, ethanol (chronic use), interferon, phenytoin, rifampin, efavirenz, nevirapine, other antiretrovirals with CYP3A4 activity ▪ Drugs that increase serum methadone level: Amitriptyline, atazanavir, atazanavir/ritonavir, cimetidine, delavirdine, diazepam, fluconazole, fluvoxamine, ketoconazole, voriconazole ▪ Opioid antagonists may precipitate withdrawal	▪ Drugs that reduce serum buprenorphine level: Ascorbic acid, barbiturates, carbamazepine, ethanol (chronic use), interferon, phenytoin, rifampin, efavirenz, nevirapine, other antiretrovirals with CYP3A4 activity ▪ Drugs that increase serum buprenorphine level: Amitriptyline, atazanavir, atazanavir/ritonavir, cimetidine, delavirdine, diazepam, fluconazole, fluvoxamine, ketoconazole, voriconazole ▪ Opioid agonist: Buprenorphine/naloxone or buprenorphine may precipitate withdrawal ▪ Opioid antagonists may precipitate withdrawal	▪ Opioid-containing medications, including over the counter preparations ▪ Thioridazine (increased lethargy and somnolence)
Monitoring		
▪ Signs of respiratory and CNS depression	▪ Liver function tests prior to initiation and during therapy	▪ Repeat liver transaminase levels at 6 and 12 months and then every 12 months thereafter

Methadone	Buprenorphine/Naloxone or Buprenorphine	Naltrexone Injectable
Patient Education		
▪ Strongly advise patient against self-medicating with CNS depressants during methadone therapy ▪ Serious overdose and death may occur if benzodiazepines, sedatives, tranquilizers, antidepressants, or alcohol are taken with methadone ▪ Store in a secure place out of the reach of children ▪ Strongly advise patient to continue in long-term methadone maintenance ▪ If discontinuing methadone, recommend transition to extended-release injectable naltrexone ▪ Serious overdose and death may occur if patient relapses to opioid use after withdrawal from methadone	▪ Strongly advise patient against self-medicating with CNS depressants during buprenorphine therapy ▪ Serious overdose and death may occur if benzodiazepines, sedatives, tranquilizers, antidepressants, or alcohol are taken with buprenorphine ▪ Store in a secure place out of the reach of children ▪ Strongly advise patient to continue in long-term buprenorphine maintenance ▪ If discontinuing buprenorphine, recommend transition to extended-release injectable naltrexone ▪ Serious overdose and death may occur if patient relapses to opioid use after withdrawal from buprenorphine	▪ Report any concerning injection site reactions ▪ Report any new or worsening depression or suicidal thinking ▪ May cause allergic pneumonia; contact provider if patient develops signs and symptoms of pneumonia ▪ If signs and symptoms of acute hepatitis occur, discontinue naltrexone and contact provider immediately ▪ Very large doses of opioids may overcome the effects of naltrexone and lead to serious injury, coma, or death ▪ Small doses of opioids, such as in analgesic, antidiarrheal, or antitussive drugs, may be blocked by naltrexone and fail to produce a therapeutic effect ▪ Patients who have previously used opioids may be more sensitive to toxic effects of opioids after discontinuation of naltrexone

Abbreviations: AUD: alcohol use disorder; CNS: central nervous system; CrCl: creatinine clearance; DSM: Diagnostic and Statistical Manual of Mental Disorders; mg: milligram(s); min: minute(s); mL: milliliter(s); OTP: Opioid Treatment Program; OUD: opioid use disorder; PDMP: prescription drug monitoring program; QTc: the heart rate corrected time from the start of the Q wave to the end of the T wave; HCG: human chorionic gonadotropin

Table B-3. Sedative-hypnotic Conversion [311-316]

Generic Name	Approximate Equivalents to Diazepam 10 mg or Phenobarbital 30 mg[1]	Time to Peak Plasma level (in Hours)	Half-life Parent Drug (in Hours)[2]	Metabolite Activity (Maximal Half-life in Hours)[3]
Alprazolam	1 mg	1-2	12 ± 2	Inactive
Chlordiazepoxide	25 mg	1-4	10 ± 3.4	Active (up to 120)
Clonazepam	1 mg	1-4	23 ± 5	Inactive
Clorazepate	15 mg	Variable	2 ± 0.9	Active (up to 120)
Diazepam	10 mg	1-2	43 ± 13	Active (up to 120)
Estazolam	1 mg	0.5-0.6	10-24	Inactive
Flurazepam	15 mg	0.5-1.0	74 ± 24	Active (up to 100)
Lorazepam	2 mg	2-4	14 ± 5	Inactive
Oxazepam	30 mg	2-3	8.0 ± 2	Inactive
Quazepam	10 mg	1.5	39	Active (up to 75)
Temazepam	15 mg	2.5	11 ± 6	Inactive
Triazolam	0.25 mg	1-2	2.9 ± 1.0	Inactive
Eszopiclone	15 mg	1	6	Active (<parent)
Zaleplon	20 mg	1	1	Inactive
Zolpidem	20 mg	1.6	2	Inactive
Butalbital	50 mg	1-2	35	Inactive
Pentobarbital	100 mg	0.5-1	15-50	Inactive
Phenobarbital	30 mg	1+	53-140	Inactive
Meprobamate	400 mg	2-3	10	Inactive
Carisoprodol	350 mg	1-3	2	Active (see Meprobamate)
Choral hydrate	250 mg	0.5	<1	Active (up to 94)

Abbreviation: mg: milligrams

[1] Withdrawal doses of diazepam or phenobarbital are those sufficient to suppress most withdrawal symptoms and may not reflect therapeutic dose equivalency.
[2] Half-life of active metabolite(s) may differ.
[3] Primary route of barbiturate elimination is renal excretion.

Appendix C: Psychosocial Interventions

Table C-1. Summary of Effectiveness of Psychosocial Interventions During Early Recovery (First 90 Days) on Condition Specific Outcomes of Substance Use Disorders (Use or Consequences) or General Psychosocial Functioning

Interventions (Alphabetical)	First-line Alternatives at Least as Effective as Other Bona Fide Active Interventions or Treatment as Usual				Added Effectiveness as Adjunctive Interventions in Combination with Pharmacotherapy and/or Other First-line Psychosocial Interventions				Comments
	Alcohol	Opioids	Stimulants/ Mixed	Cannabis	Alcohol	Opioids	Stimulants/ Mixed	Cannabis	
Behavioral Couples Therapy (BCT)	√	N/A	N/A	N/A	?	N/A	N/A	N/A	Effective for male or female SUD patients and partners; improves marital satisfaction
Cognitive Behavioral Coping Skills Training	√	N/A	√	√	√	√/?	N/A	√	Added benefit in methadone treatment; Unclear added benefit of CBT in some studies of office-based buprenorphine
Contingency Management (CM)/ Motivational Incentives	N/A	N/A	N/A	N/A	?	√	√	√	CM is recommended only as an adjunctive treatment. CM for cannabis may be problematic given slow clearance in urine
Community Reinforcement Approach (CRA)	√	N/A	√	N/A	N/A	N/A	N/A	N/A	Complex intervention best when including CM
Individual Drug Counseling	N/A	N/A	N/A	N/A	N/A	N/A	√	N/A	One study found benefit when combined with group drug counseling
Motivational Enhancement Therapy (MET)	√	N/A	N/A	√	√	N/A	?	?	Some evidence for those with AUD and low readiness or high anger
12-Step Facilitation (TSF)	√	N/A	N/A	N/A	√	N/A	N/A	N/A	12-step involvement is instrumental in explaining TSF benefits

Symbols: √: Good confidence in effectiveness; ?: Questionable confidence in effectiveness; N/A: Insufficient evidence
Abbreviations: AUD: alcohol use disorder

A. Behavioral Couples Therapy

Most versions of BCT are focused both on reducing alcohol or drug use in the identified patient and on improving overall marital satisfaction for both partners. In BCT sessions, the therapist arranges a daily sobriety contract in which the patient states his or her intent not to drink or use drugs that day, and the partner expresses support for the patient's efforts to stay abstinent. The Sobriety Contract can also include

urine drug screens for the patient, attendance at other agreed-to counseling sessions, or 12-step meetings by the patient and partner. To improve relationship functioning, BCT uses a series of behavioral assignments to increase positive feelings, shared activities, and constructive communication because these relationship factors are conducive to sobriety.[317,318]

B. Cognitive-Behavioral Coping Skills Therapy

Cognitive-behavioral coping skills therapy consists of related treatment approaches for SUD that focus on teaching patients to modify both thinking and behavior related not only to substance use, but to other areas of life functionally related to substance use. Patients learn to track their thinking and activities and identify the affective and behavioral consequences of those thoughts and activities. Patients then learn techniques to change thinking and behaviors that contribute to substance use, and to strengthen coping skills, improve mood, interpersonal functioning and enhance social support. Primary therapeutic techniques include education of the patient about the treatment model, collaboration between the patient and therapist to choose goals, identifying unhelpful thoughts and developing experiments to test the accuracy of such thoughts, guided discovery (facilitating the patient in identifying alternative beliefs through the use of questions designed to explore current beliefs), interpersonal skill building through communication and assertiveness training, behavioral rehearsal, and role-play. In addition, treatment incorporates structured practice outside of session, including scheduled activities, self-monitoring, thought recording and challenging, and interpersonal skills practice.[121,319-321]

C. Community Reinforcement Approach

CRA is a comprehensive cognitive-behavioral intervention for the treatment of SUD by focusing on environmental contingencies that impact and influence the patient's behavior. Developed in accordance with the belief that these environmental contingencies play a crucial role in an individual's addictive behavior and recovery, CRA utilizes familial, social, recreational, and occupational events to support the individual in changing his or her drinking/using behaviors and in creating a successful sobriety. The goal is to rearrange multiple aspects of an individual's life so that a sober lifestyle is more rewarding than one that is dominated by alcohol and/or drugs. CRA integrates several treatment components, including building the patient's motivation to quit drinking/using, helping the patient initiate sobriety, analyzing the patient's drinking/using pattern, increasing positive reinforcement, learning new coping behaviors, and involving significant others in the recovery process.[322,323]

D. Contingency Management for Substance Use Disorders Treatment

CM approaches are based on behavioral principles of reinforcement that reward specific behavioral goals related to recovery. Either monetary or nonmonetary rewards are made contingent on objective evidence such as negative toxicology results (e.g., biological tests for recent drug or alcohol use), treatment adherence, or progress toward treatment goals. The most common form of contingencies provided to reinforce desired behaviors are vouchers with monetary value that can be redeemed for goods and services, specific material prizes, or draws from a "fishbowl" that contains cards which vary in their reinforcing value from simple praise to vouchers worth $1 to $100. Schedules (fixed or intermittent) and magnitude of reinforcement have varied and have implications for overall cost of clinical implementation.[324]

E. Individual Drug Counseling

The approach to individual drug counseling is manualized [325] and includes patient education about a biopsychosocial and spiritual approach to recovery, attention to building a therapeutic alliance, monitored urine drug testing and encouragement of 12-step (e.g., Alcoholics Anonymous [AA], Narcotics Anonymous [NA]) participation.

F. Motivational Enhancement Therapy

MET is a less intensive form of specialized psychosocial intervention for patients with SUD. MET uses principles of motivational interviewing (MI) including an empathic, client-centered, but directive, approach intended to heighten awareness of ambivalence about change, promote commitment to change, and enhance self-efficacy. MET differs from MI in that it is a more structured intervention that is based to a greater degree on systematic assessment with personalized feedback. The therapeutic style using MI elicits client reactions to assessment feedback, commitment to change, and collaboration on development of an individualized change plan. Involvement of a significant other is encouraged in at least one of the MET sessions.[326]

G. 12-Step Facilitation

TSF therapy aims to increase the patient's active involvement in AA or other 12-step based mutual help groups. This approach was systematized in a manual for National Institute on Alcohol Abuse and Alcoholism's (NIAAA's) Project MATCH and delivered as 12-sessions of individual therapy in which the therapist actively encourages engagement in AA, and walks the patient through the first four steps of the AA program. The therapist conveys the concept that addiction is a chronic, progressive, and potentially fatal illness for which the only successful strategy is abstinence achieved one day at a time by following a 12-step program of recovery. Each therapy session is divided into three parts. The first part reviews relevant events of the last week (including urges to use, drinking behavior and recovery-oriented activities) and a homework assignment. The middle portion introduces new material related to the 12-steps. The conclusion of the session includes a homework assignment and development of a plan for recovery-oriented activities (meeting attendance, sponsor contact).[327]

Appendix D: Evidence Table

Recommendation	2009 Grade[1]	Evidence[2]	Strength of Recommendation[3]	Recommendation Category[4]
1. For patients in general medical and mental healthcare settings, we recommend screening for unhealthy alcohol use annually using the three-item Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) or Single Item Alcohol Screening Questionnaire (SASQ).	A, A, A, B, None, A	[65-70,72,73] **Additional References:** [71,74-81]	Strong For	Not reviewed, Amended
2. For patients without documented alcohol use disorder who screen positive for unhealthy alcohol use, we recommend providing a single initial brief intervention regarding alcohol-related risks and advice to abstain or drink within nationally established age and gender-specific limits for daily and weekly consumption.	A	[65,66,82-84,91-99] **Additional References:** [85-90,100,101]	Strong For	Reviewed, New-replaced
3. For patients with a diagnosis of a substance use disorder, we suggest offering referral for specialty substance use disorder care based on willingness to engage in specialty treatment.	None, B, None, None, A, None, None, None	[44] **Additional References:** [21,106,107]	Weak For	Not reviewed, Amended

[1] The 2009 VA/DoD SUD CPG used the USPSTF evidence grading system (http://www.uspreventiveservicestaskforce.org). Inclusion of more than one 2009 Grade indicates that more than one 2009 CPG recommendation is covered under the 2015 recommendation. The strength of recommendations were rated as follows: A- a strong recommendation that the clinicians provide the intervention to eligible patients; B- a recommendation that clinicians provide (the service) to eligible patients; C- no recommendation for or against the routine provision of the intervention is made; D- recommendation is made against routinely providing the intervention; I- the conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention.

[2] The evidence column indicates studies that support each recommendation. For new recommendations, developed by the 2015 guideline Work Group, the literature cited corresponds directly to the 2015 evidence review. For recommendations that have been carried over from the 2009 VA/DoD SUD CPG, slight modifications were made to the language in order to better reflect the current evidence and/or the change in grading system used for assigning the strength of each recommendation (USPSTF to GRADE). For these "modified" recommendations, the evidence column indicates "additional evidence," which can refer to either 1) studies that support the recommendation and which were identified through the 2015 evidence review, or 2) relevant studies that support the recommendation, but which were not systematically identified through a literature review.

[3] Refer to the Grading Recommendations section for more information on how the strength of the recommendation was determined using GRADE methodology.

[4] Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.

Recommendation	2009 Grade[1]	Evidence[2]	Strength of Recommendation[3]	Recommendation Category[4]
4. For patients with substance use disorders, there is insufficient evidence to recommend for or against using a standardized assessment that would determine initial intensity and setting of substance use disorder care rather than the clinical judgment of trained providers.	B	**Additional References:** [108]	N/A	Reviewed, New-replaced
5. For patients with moderate-severe alcohol use disorder, we recommend offering one of the following medications: • Acamprosate • Disulfiram • Naltrexone- oral or extended release • Topiramate	None, None, None, None, A, A, A	[109-112,114] **Additional References:** [113,115]	Strong For	Reviewed, New-replaced
6. For patients with moderate-severe alcohol use disorder for whom first-line pharmacotherapy is contraindicated or ineffective, we suggest offering gabapentin.	None, None, None, None, A, A, A	[112,116,118] **Additional References:** [117]	Weak For	Reviewed, New-replaced
7. For patients with alcohol use disorder we recommend offering one or more of the following interventions considering patient preference and provider training/competence: • Behavioral Couples Therapy for alcohol use disorder • Cognitive Behavioral Therapy for substance use disorders • Community Reinforcement Approach • Motivational Enhancement Therapy • 12-Step Facilitation	None, A	[119-131]	Strong For	Reviewed, New-replaced
8. For patients with opioid use disorder, we recommend offering one of the following medications considering patient preferences: • Buprenorphine/naloxone • Methadone in an Opioid Treatment Program	None, None, A, A	[133,135-137,139-148,151,156,158] **Additional References:** [132,134,138,149,150,152-155,157,171,172]	Strong For	Reviewed, New-replaced

Recommendation	2009 Grade[1]	Evidence[2]	Strength of Recommendation[3]	Recommendation Category[4]
9. In pregnant women with opioid use disorder for whom buprenorphine is selected, we suggest offering buprenorphine alone (i.e., without naloxone) considering patient preferences.	--	[139,166] **Additional References:** [159-165,167-169]	Weak For	Reviewed, New-added
10. For patients with opioid use disorder for whom buprenorphine is indicated, we recommend individualizing choice of appropriate treatment setting (i.e., Opioid Treatment Program or office-based) considering patient preferences.	None	**Additional References:** [170]	Strong For	Reviewed, New-replaced
11. For patients with opioid use disorder for whom opioid agonist treatment is contraindicated, unacceptable, unavailable, or discontinued and who have established abstinence for a sufficient period of time (see narrative), we recommend offering: • Extended-release injectable naltrexone	None, None	[173] **Additional References:** [174]	Strong For	Reviewed, New-replaced
12. There is insufficient evidence to recommend for or against oral naltrexone for treatment of opioid use disorder.	None, None	[136,176,177] **Additional References:** [175]	N/A	Reviewed, New-replaced
13. At initiation of office-based buprenorphine, we recommend addiction-focused Medical Management (see narrative) alone or in conjunction with another psychosocial intervention.	C, A, A	[51-54,178] **Additional References:** [55]	Strong For	Reviewed, New-replaced
14. For patients in office-based buprenorphine treatment, there is insufficient evidence to recommend for or against any specific psychosocial interventions in addition to addiction-focused Medical Management. Choice of psychosocial intervention should be made considering patient preferences and provider training/competence.	None, A	[51,181,182] **Additional References:** [179,180]	N/A	Reviewed, New-replaced
15. In Opioid Treatment Program settings, we suggest offering individual counseling and/or Contingency Management, considering patient preferences and provider training/competence.	A	[183,184,187,188,191,192] **Additional References:** [170,185,186,189,190]	Weak For	Reviewed, New-replaced

Recommendation	2009 Grade[1]	Evidence[2]	Strength of Recommendation[3]	Recommendation Category[4]
16. For patients with opioid use disorder for whom opioid use disorder pharmacotherapy is contraindicated, unacceptable or unavailable, there is insufficient evidence to recommend for or against any specific psychosocial interventions.	None, A	[53] **Additional References:** [193]	N/A	Reviewed, New-replaced
17. There is insufficient evidence to recommend for or against the use of pharmacotherapy in the treatment of cannabis use disorder.	--	[194-198]	N/A	Reviewed, New-added
18. For patients with cannabis use disorder, we recommend offering one of the following interventions as initial treatment considering patient preference and provider training/competence: • Cognitive Behavioral Therapy • Motivational Enhancement Therapy • Combined Cognitive Behavioral Therapy/Motivational Enhancement Therapy	None	[199-203]	Strong For	Reviewed, New-replaced
19. There is insufficient evidence to recommend for or against the use of any pharmacotherapy for the treatment of cocaine use disorder or methamphetamine use disorder.	--	[204,206-210,212] **Additional References:** [205,211]	N/A	Reviewed, New-added
20. For patients with stimulant use disorder, we recommend offering one or more of the following interventions as initial treatment considering patient preference and provider training/competence: • Cognitive Behavioral Therapy • Recovery-focused behavioral therapy ◆ General Drug Counseling ◆ Community Reinforcement Approach • Contingency Management in combination with one of the above	None	[213,217-220,222,226,229,230] **Additional References:** [214-216,221,223-225,227,228,231]	Strong For	Reviewed, New-replaced

Recommendation	2009 Grade[1]	Evidence[2]	Strength of Recommendation[3]	Recommendation Category[4]
21. For patients with substance use disorders in early recovery or following relapse, we recommend promoting active involvement in group mutual help programs using one of the following systematic approaches considering patient preference and provider training/competence: • Peer linkage • Network support • Twelve-step facilitation	None, A	[235,239] **Additional References:** [232-234,236-238]	Strong For	Reviewed, New-replaced
22. Among patients in early recovery from substance use disorders or following relapse, we suggest prioritizing other needs through shared decision making (e.g., related to other mental health conditions, housing, supportive recovery environment, employment, or related recovery-relevant factors) among identified biopsychosocial problems and arranging services to address them.	B, None, None, None, None, None, None, None, B, None, None	[240-242]	Weak For	Not reviewed, Amended
23. We suggest assessing response to treatment periodically and systematically, using standardized and valid instrument(s) whenever possible. Indicators of treatment response include ongoing substance use, craving, side effects of medication, emerging symptoms, etc.	None, None, None, A, None, None, None, None, None, None, None, None	[243,244]	Weak For	Reviewed, New-replaced
24. For patients who have initiated an intensive phase of outpatient or residential treatment, we recommend offering and encouraging ongoing systematic relapse prevention efforts or recovery support individualized on the basis of treatment response.	None	[248,249] **Additional References:** [245-247,250]	Strong For	Not reviewed, Amended
25. For patients in substance use disorders specialty care, we recommend against automatic discharge from care for patients who do not respond to treatment or who relapse.	None	[249] **Additional References:** [250-253]	Strong Against	Not reviewed, Amended
26. For patients with alcohol or opioid use disorder in early abstinence, we suggest using standardized measures to assess the severity of withdrawal symptoms such as Clinical Institute Withdrawal Assessment for Alcohol (revised version) (CIWA-Ar) for alcohol or Clinical Opiate Withdrawal Scale (COWS) for opioids.	B	[260,262,269,270] **Additional References:** [254-259,261,263-268,271]	Weak For	Not reviewed, Amended

Recommendation	2009 Grade[1]	Evidence[2]	Strength of Recommendation[3]	Recommendation Category[4]
27. We recommend inpatient medically supervised alcohol withdrawal management for patients with any of the following conditions: • History of delirium tremens or withdrawal seizures • Inability to tolerate oral medication • Co-occurring medical conditions that would pose serious risk for ambulatory withdrawal management (e.g., severe coronary artery disease, congestive heart failure, liver cirrhosis) • Severe alcohol withdrawal (i.e., Clinical Institute Withdrawal Assessment for Alcohol [revised version] [CIWA-Ar] score ≥20) • Risk of withdrawal from other substances in addition to alcohol (e.g., sedative hypnotics)	None, C	[272] **Additional References:** [273,274]	Strong For	Reviewed, Amended
28. We suggest inpatient medically supervised withdrawal for patients with symptoms of at least moderate alcohol withdrawal (i.e., Clinical Institute Withdrawal Assessment for Alcohol [revised version] [CIWA-Ar] score ≥10) and any of the following conditions: • Recurrent unsuccessful attempts at ambulatory withdrawal management • Reasonable likelihood that the patient will not complete ambulatory withdrawal management (e.g., due to homelessness) • Active psychosis or severe cognitive impairment • Medical conditions that could make ambulatory withdrawal management problematic (e.g., pregnancy, nephrotic syndrome, cardiovascular disease, lack of medical support system)	C	[272] **Additional References:** [273,274]	Weak For	Reviewed, Amended
29. We recommend using one of the following pharmacotherapy strategies for managing alcohol withdrawal symptoms: • A predetermined fixed medication tapering schedule with additional medication as needed • Symptom-triggered therapy where patients are given medication only when signs or symptoms of withdrawal occur (e.g., as needed dosing)	A, B	[262,275] **Additional References:** [276,277]	Strong For	Not reviewed, Amended

Recommendation	2009 Grade[1]	Evidence[2]	Strength of Recommendation[3]	Recommendation Category[4]
30. For treatment of moderate to severe alcohol withdrawal, we recommend using benzodiazepines with adequate monitoring because of documented efficacy and high margin of safety.	A	[278,279,281] **Additional References:** [280,282]	Strong For	Reviewed, Amended
31. For managing mild to moderate alcohol withdrawal in patients for whom risks of benzodiazepines outweigh benefits (e.g., inadequate monitoring available, abuse liability, or allergy/adverse reactions), we suggest considering carbamazepine, gabapentin, or valproic acid as an alternative.	B	[278,281] **Additional References:** [280,282]	Weak For	Reviewed, New-replaced
32. We recommend against using alcohol as an agent for medically supervised withdrawal.	D	**Additional References:** [283-286]	Strong Against	Not reviewed, Amended
33. For patients not yet stabilized from opioid use disorder, we recommend against withdrawal management alone due to high risk of relapse and overdose (see Recommendations 8 and 11).	B	[137,151,290,296] **Additional References:** [152-154,288,289,291-295,297-300]	Strong Against	Reviewed, New-Replaced
34. Among patients with opioid use disorder for whom maintenance agonist treatment is contraindicated, unacceptable, or unavailable, we recommend using a methadone (in Opioid Treatment Program only) or buprenorphine taper for opioid withdrawal management (see Recommendation 11).	None	[287,296] **Additional References:** [179,180]	Strong For	Reviewed, New-replaced
35. For patients with opioid use disorder for whom methadone and buprenorphine are contraindicated, unacceptable, or unavailable, we recommend offering clonidine as a second-line agent for opioid withdrawal management (see Recommendation 11).	None	[301-303] **Additional References:** [179,180]	Strong For	Reviewed, New-replaced
36. For patients in need of withdrawal management for sedative hypnotics, we suggest one of the following: • Gradually taper the original benzodiazepine • Substitute a longer acting benzodiazepine then taper gradually • Substitute phenobarbital for the addicting agent and taper gradually	A, None, None	**Additional References:** [304-307]	Weak For	Not Reviewed, Amended

Appendix E: 2009 Recommendation Categorization Table

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
A	B	1	Patients in general and mental healthcare settings should be screened for unhealthy alcohol use annually.	A	Not reviewed, Amended	Recommendation 1
A	B	2	Use a validated screening questionnaire for past-year unhealthy alcohol use.	A	Not reviewed, Amended	Recommendation 1
A	B	3	Select one of two brief methods of screening: ■ The Alcohol Use Disorders Identification Test Consumption Questions (AUDIT-C) or ■ Ask whether patient drank any alcohol in the past year and administer the Single-Item Alcohol Screening Questionnaire (SASQ) to assess the frequency of heavy drinking in patients who report any drinking. (see Annotation C)	A	Not reviewed, Amended	Recommendation 1
A	B	4	The CAGE questionnaire alone is not a recommended screen for past-year unhealthy alcohol use (e.g., risky or hazardous drinking).	D	Not reviewed, Deleted	--
A	B	5	The CAGE questionnaire, used as a self-assessment tool, may be used in addition to an appropriate screening method to increase patient's awareness to unhealthy use or abuse of alcohol.	None	Not reviewed, Deleted	--
A	C	1	Consider a screen positive for unhealthy alcohol use if: ■ AUDIT-C score (range from 0 to 12) is > 4 points for men or > 3 points for women	B	Not reviewed, Amended	Recommendation 1

[1] The first three columns indicate the location of each recommendation within the 2009 SUD CPG.

[2] The 2009 Recommendation Text column contains the wording of each recommendation from the 2009 SUD CPG.

[3] The 2009 VA/DoD SUD CPG used the U.S. Preventive Services Task Force (USPSTF) evidence grading system. http://www.uspreventiveservicestaskforce.org The strength of recommendations were rated as follows: A- a strong recommendation that the clinicians provide the intervention to eligible patients; B- a recommendation that clinicians provide (the service) to eligible patients; C- no recommendation for or against the routine provision of the intervention is made; D- recommendation is made against routinely providing the intervention; I- the conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention.

[4] The Category column indicates the way in which each 2009 SUD CPG recommendation was updated.

[5] For recommendations that were carried forward to the 2015 SUD CPG, this column indicates the new recommendation(s) to which they correspond.

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
			▪ Patients report drinking 4 or more (women) or 5 or more (men) drinks in a day in the past year on the single-item screening question.			
A	C	2	Identify contraindications for any alcohol use . Contraindications to alcohol use include: ▪ Pregnancy or trying to conceive ▪ Liver disease including hepatitis C ▪ Other medical conditions potentially exacerbated or complicated by drinking (e.g., pancreatitis, congestive heart failure) ▪ Use of medications with clinically important interactions with alcohol or intoxication (e.g., warfarin) ▪ An alcohol use disorder	C	Not reviewed, Deleted	--
A	D	1	Determine the number of drinks consumed by the patient in a typical week and the maximum number of drinks on an occasion in the past month.	None	Not reviewed, Amended	Recommendation 1
A	E	1	Determine whether patient drinks above recommended limits. ▪ The recommended limits are: • For men— no more than 14 standard-sized drinks a week and no more than 4 standard-sized drinks on any day • For women— no more than 7 standard-sized drinks a week and no more than 3 standard-sized drinks on any day ▪ Standard-sized drinks are: 12 oz beer, 5 oz wine, or 1.5 oz hard liquor.	A	Not reviewed, Amended	Recommendation 1
A	E	2	Contraindications for any alcohol use include: ▪ Pregnancy or trying to conceive ▪ Liver disease including hepatitis C ▪ Other medical conditions potentially exacerbated or complicated by drinking (e.g., pancreatitis, congestive heart failure) ▪ Use of medications with clinically important interactions with alcohol or intoxication (e.g., warfarin) ▪ An alcohol use disorder.	None	Not reviewed, Deleted	--

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
A	F	1	Provide a brief intervention (counseling) for alcohol use, which includes the following components: ■ Express concern that the patient is drinking at unhealthy levels known to increase his/her risk of alcohol-related health problems ■ Provide feedback linking alcohol use and health, including: • Personalized feedback (i.e., explaining how alcohol use can interact with patient's medical concerns [hypertension, depression/anxiety, insomnia, injury, congestive heart failure (CHF), diabetes mellitus (DM), breast cancer risk, interactions with medications]); or • General feedback on health risks associated with drinking ■ Advise: • To abstain (if there are contraindications to drinking); or • To drink below recommended limits (specified for patient). ■ Support the patient in choosing a drinking goal, if he/she is ready to make a change ■ Offer referral to specialty addictions treatment if appropriate	A	Reviewed, New-replaced	Recommendation 2
A	G	1	Offer referral to specialty SUD care for addiction treatment if the patient: ■ May benefit from additional evaluation of his/her drinking or substance use and related problems or from motivational interviewing ■ Has tried and been unable to change drinking or substance use on his/her own or does not respond to brief intervention ■ Has been diagnosed for alcohol or other substance dependence ■ Has previously been treated for an alcohol or other substance use disorders ■ Has an AUDIT-C score > 8	None	Not reviewed, Amended	Recommendation 3
A	G	2	DoD active duty members involved in an incident in which substance use is suspected to be a contributing factor are required to be referred to specialty SUD care for evaluation. Command should be contacted to discuss administrative and clinical options if the member refuses to be evaluated. (Repeated in other sections)	None	Not reviewed, Deleted	--

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
A	H	1	Agree on a set of specific goals with the patient. ■ Review with the patient results of previous efforts of self-change and formal treatment experience, including reasons for treatment dropout ■ Ask patient about willingness to accept referral ■ Consider bringing an addiction specialist into a general medical or mental health visit to assist with referral decision	None	Not reviewed, Deleted	--
A	H	2	Patients at high risk for alcohol use disorder but who are not ready for specialty addictions treatment should be engaged in monitoring of alcohol-related medical problems in the medical setting.	None	Not reviewed, Deleted	--
A	H	3	DoD active duty members involved in an incident in which substance use is suspected to be a contributing factor are required to be referred to specialty SUD care for evaluation. Command should be contacted to discuss administrative and clinical options if the member refuses to be evaluated (see Appendix D).	None	Not reviewed, Deleted	--
A	I	1	Address alcohol at the next medical visit scheduled to address other issues, or schedule a separate appointment to specifically address drinking if the patient agrees.	B	Not reviewed, Deleted	--
A	I	2	Repeat brief intervention at the follow-up visit if the patient has not responded to a previous brief intervention.	B	Reviewed, Deleted	--
A	J	1	Provide positive feedback to patients for decreases in drinking.	None	Not reviewed, Deleted	--
A	J	2	Relate changes in drinking to any changes in presenting health conditions.	None	Not reviewed, Deleted	--
A	K	1	Advise patients who screen positive for unhealthy alcohol use but who report drinking below recommended limits to continue to drink below recommended limits.	None	Not reviewed, Deleted	--
A	L	1	Repeat alcohol screening annually.	None	Not reviewed, Deleted	--
B	B	1	Assure patient safety and readiness to cooperate with further assessment by referring the patient to an emergency department or appropriate setting for stabilization as needed.	None	Not reviewed, deleted	--

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
B	C	1	Obtain a comprehensive biopsychosocial assessment that includes all of the following:* ■ History of the present episode, including precipitating factors, current symptoms and pertinent present risks: • Family history: Family alcohol and drug use history, including past treatment episodes; Family social history, including profiles of parents (or guardians or other caretakers), home atmosphere, economic status, religious affiliation, cultural influences, leisure activities, monitoring and supervision, and relocations; Family medical and psychiatric history • Developmental history, including pregnancy and delivery, developmental milestones and temperament • Comprehensive substance use history, including onset and pattern of progression, past sequelae and past treatment episodes (include all substances, e.g., alcohol, illicit drugs, tobacco, caffeine, over-the-counter medications, prescription medications, inhalants) • Nearly all daily nicotine users are nicotine dependent. Identification and treatment of co-morbid nicotine dependence may improve recovery rates of other SUDs. For patients using nicotine, offer and recommend tobacco use cessation treatment. Use the Clinical Practice Guideline: Treating Tobacco Use Dependence: 2008 Update from the U.S. Department of Health and Human Services available at: http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf and the VA/DoD Clinical Practice Guideline for Management of Tobacco Use • Recent pattern of substance use based on self-report and urine drug screening • Personal/social history (including housing issues, religious/spiritual affiliation, cultural influences) • School history • Military history • Marital history • Peer relationships and friendships • Leisure activities • Sexual activity • Physical or sexual abuse • Legal/non-judicial punishment history, including past behaviors and their relation to substance use, arrests, adjudications and details of current status • Psychiatric history, including symptoms and their relation to substance use, current and past diagnoses, treatments and providers	None	Not reviewed, Deleted	--

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
			• Medical history, including pertinent medical problems and treatment, surgeries, head injuries, present medications and allergies • Review of systems, including present and past medical and psychological symptoms ■ Laboratory tests for infectious diseases (HIV, Hepatitis C, sexually transmitted disease) and consequences of substance use (e.g., liver function tests) ■ Mental status examination ■ Survey of assets, vulnerabilities and supports ■ Patient's perspective on current problems, treatment goals and preferences *Adapted from ASAM Patient Placement Criteria, 2nd Edition-Revised (ASAM PPC-2R, 2001)			
B	C	2	Use empathic and non-judgmental (versus confrontational) therapist style, being sensitive to gender, cultural and ethnic differences.	None	Not reviewed, Deleted	--
B	D	1	Provide a narrative to consolidate and interpret the information obtained during the assessment process.	None	Not reviewed, Deleted	--
B	D	2	Include a diagnostic formulation.	None	Not reviewed, Deleted	--
B	D	3	Include past treatment response and patient's perspective on current problems.	None	Not reviewed, Deleted	--
B	D	4	Review the patient's motivational level, treatment preferences and goals, and consider these factors, along with an interdisciplinary perspective and available programming, in recommending specific treatment options.	B	Not reviewed, Amended	Recommendation 3
B	D	5	Present and discuss the treatment options with the patient and significant others.	None	Not reviewed, Deleted	--
B	D	6	Determine whether the treatment plan can be implemented in general health care (including primary care) based on availability of a willing provider, severity and chronicity of the SUD, active involvement with recovery supports in the community, prior treatment response, and patient preference and likelihood of adherence.	None	Not reviewed, Amended	Recommendation 3
B	D	7	If treatment in specialty SUD care is appropriate, determine the appropriate initial intensity and level of specialty SUD care, based on ASAM patient placement criteria.	B	Reviewed, New-replaced	Recommendation 4
B	D	8	If treatment in specialty SUD care is recommended, determine if it is an acceptable mode of treatment to the patient.	None	Not reviewed, Deleted	--

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
B	D	9	Involve the patient in prioritizing problems to be addressed in the initial treatment plan, and in selecting specific treatment goals, regardless of the level of care selected (see Table B-1).	None	Not reviewed, Deleted	--
B	D	10	If the patient does not agree to the treatment plan, provide motivational intervention and offer to renegotiate the treatment plan.	None	Not reviewed, Deleted	--
B	D	11	*For DoD Active Duty Members:* A treatment team shall convene with the patient and command to review the treatment plan and goals.	None	Not reviewed, Deleted	--
B	E	1	Discuss addiction-focused pharmacotherapy options with all patients with opioid and/or alcohol dependence.	None	Reviewed, New-replaced	Recommendation 5 Recommendation 6 Recommendation 8 Recommendation 11 Recommendation 12
B	E	2	Initiate addiction-focused pharmacotherapy if indicated and monitor adherence and treatment response.	None	Reviewed, New-replaced	Recommendation 5 Recommendation 6 Recommendation 8 Recommendation 11 Recommendation 12
B	F	1	Indicate to the patient and significant others that treatment is more effective than no treatment (i.e., "Treatment works").	None	Not reviewed, Deleted	--
B	F	2	Consider the patient's prior treatment experience and respect patient preference for the initial psychosocial intervention approach, since no single intervention approach has emerged as the treatment of choice.	None	Not reviewed, Deleted	--
B	F	3	Regardless of the particular psychosocial intervention chosen, use motivational interviewing style during therapeutic encounters with patients and emphasize the common elements of effective interventions including: enhancing patient motivation to stop or reduce substance use, improving self-efficacy for change, promoting a therapeutic relationship, strengthening coping skills, changing reinforcement contingencies for recovery, and enhancing social support for recovery.	None	Not reviewed, Deleted	--
B	F	4	Emphasize that the most consistent predictors of successful outcome are retention in formal treatment and/or active involvement with community support for recovery.	None	Not reviewed, Deleted	--

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
B	F	5	Use strategies demonstrated to be efficacious to promote active involvement in available mutual help programs (e.g., Alcoholics Anonymous, Narcotics Anonymous).	None	Reviewed, New-replaced	Recommendation 21
B	F	6	Based on locally available expertise, initiate addiction-focused psychosocial interventions with empirical support. Consider the following interventions that have been developed into published treatment manuals and evaluated in randomized trials: ■ Behavioral Couples Counseling ■ Cognitive Behavioral Coping Skills Training ■ Community Reinforcement Approach ■ Contingency Management/Motivational Incentives ■ Motivational Enhancement Therapy ■ Twelve-Step Facilitation.	None	Reviewed, New-replaced	Recommendation 7 Recommendation 14 Recommendation 15 Recommendation 16 Recommendation 18 Recommendation 20
B	F	7	Addiction-focused psychosocial interventions should be coordinated with evidence-based intervention(s) for other biopsychosocial problems to address identified concurrent problems.	None	Reviewed, Deleted	--
B	F	8	Intervention should be provided in the least restrictive setting necessary for safety and effectiveness.	None	Reviewed, Deleted	--
B	G	1	Prioritize and address other coexisting biopsychosocial problems with services targeted to these problem areas, rather than increasing intensity of addiction-focused psychosocial treatment alone.	B	Not reviewed, Amended	Recommendation 22
B	G	2	Address transitional housing needs to facilitate access to treatment and promote a supportive recovery environment.	None	Not reviewed, Amended	Recommendation 22
B	G	3	Provide social/vocational/legal services in the most accessible setting to promote engagement and coordination of care.	None	Not reviewed, Amended	Recommendation 22
B	G	4	Address deferred problems as part of treatment plan updates and monitor emerging needs.	None	Not reviewed, Amended	Recommendation 22
B	G	5	Coordinate care with other social service providers or case managers.	None	Not reviewed, Amended	Recommendation 22
B	H	1	Prioritize and address other medical and psychiatric co-occurring conditions.	None	Not reviewed, Deleted	--

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
B	H	2	Recommend and offer cessation treatment to patients with nicotine dependence.	None	Not reviewed, Deleted	--
B	H	3	Treat concurrent psychiatric disorders consistent with VA/DoD clinical practice guidelines (e.g., Major Depressive Disorder, Bipolar Disorder, Post Traumatic Stress, Psychoses) including concurrent pharmacotherapy.	None	Not reviewed, Deleted	--
B	H	4	Provide or arrange treatment via referral for medical conditions (e.g. management of diabetes, chronic heart failure, management of unexplained medical symptoms). (See other VA/DoD Clinical Practice Guidelines at: www.healthquality.va.gov)	None	Not reviewed, Deleted	--
B	H	5	Provide multiple services in the most accessible setting to promote engagement and coordination of care.	None	Not reviewed, Deleted	--
B	H	6	Monitor and address deferred problems and emerging needs through ongoing treatment plan updates.	None	Not reviewed, Amended	Recommendation 22
B	H	7	Coordinate care with other providers.	None	Not reviewed, Amended	Recommendation 22
B	I	1	Reassess and document clinical response throughout the course of treatment: ■ Daily in the acute inpatient setting, including reevaluation of the continued need for that level of care. ■ At least weekly in the residential setting, including reevaluation of the continued need for that level of care. ■ In the outpatient setting: • Weekly during the first few weeks for a new episode of care • At least monthly thereafter.	None	Reviewed, New-replaced	Recommendation 23
B	J	1	For patients who accomplish their initial goals in early recovery, the treatment team should collaborate with the patient to develop a continuing care plan (e.g., aftercare plan) which may include: ■ Transition to an appropriate alternative specialty care setting (see Annotation L - Aftercare), such as PTSD specialty treatment, etc. ■ Return to primary care.	None	Not reviewed, Deleted	--

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
B	J	2	For patients who are progressing toward goals, providers should: ■ Provide positive feedback and encouragement to remain engaged in specialty SUD care ■ Involve patients in identifying the next interim steps toward achieving the goals. Consider reduced treatment intensity or discontinuing some treatment components based on: ■ Accomplishment of treatment goals and objectives ■ Full, early remission ■ Early problem resolution ■ Greater involvement in community support ■ Improvements in other associated problem areas. Coordinate follow-up with the patient's primary medical or behavioral health provider during transitions to less intensive levels of care in order to reinforce progress and improve monitoring of relapse risks.	None	Not reviewed, Deleted	--
B	K	1	Use the patient's progress in attaining recovery goals to individualize treatment continuation and avoid adopting uniform treatment plans with standardized duration and intensity.	None	Reviewed, New-replaced	Recommendation 23
B	K	2	Consider patient report of craving and other subjective indications of relapse risk.	None	Reviewed, New-replaced	Recommendation 23
B	K	3	For patients who achieve sustained remission or problem resolution, provide appropriate continuity of care and follow-up with providers in the general medical or mental health care setting (see Module C).	None	Not reviewed, Deleted	--
B	L	1	Provide continuing care following intensive outpatient or residential rehabilitation (individual, group or telephone follow-up).	None	Not reviewed, Amended	Recommendation 24
B	L	2	Consider objective monitoring of substance use and medical consequences.	A	Reviewed, New-replaced	Recommendation 23
B	L	3	Encourage active involvement in community support for recovery (e.g., Alcoholics Anonymous, Cocaine Anonymous).	A	Reviewed, New-replaced	Recommendation 21

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
B	L	4	As part of the discharge instructions from the intensive phase, provide the patient a written plan to facilitate compliance with aftercare which may include "the basic things I need to do to meet my treatment goals," such as: ■ Information on treatment appointments and prescribed medications ■ Recognizing relapse warning signs and triggers and appropriate coping responses ■ Maintaining contact with recovery support network and identifying mutual help meetings to attend.	None	Reviewed, Deleted	--
B	L	5	For DoD Active Duty: Rehabilitation and Referral Services for Alcohol and Drug Abusers, requires an individualized aftercare plan designed to identify the continued support of the patient with monthly monitoring (minimally) during the first year after inpatient treatment.	None	Not reviewed, Deleted	--
B	M	1	For patients who are not improving, providers should consider either: ■ Adding or substituting another medication or psychosocial intervention, or ■ Changing treatment intensity by: • Increasing the intensity of care, or • Increasing the dose of the medication, or • Decreasing the intensity to a minimum level of care that is agreeable to the patient such as monitoring in general health care (see Module C).	None	Not reviewed, Amended	Recommendation 25
B	M	2	If patients drop out of treatment, the treatment team should make efforts to contact the patient and re-engage him/her in treatment.	None	Not reviewed, Deleted	--
C	B	1	Assure patient safety and readiness to cooperate with further assessment by referring the patient to an emergency department or appropriate acute care setting for stabilization as needed.	None	Not reviewed, deleted	--
C	C	1	Patients with suspected, presumed, or identified substance use disorder (SUD) should receive a comprehensive assessment to include: ■ Medical history, including pertinent medical problems and treatment, surgeries, head injuries, present medications and allergies and family history of substance use ■ Physical examination including mental status examination (MSE) ■ Laboratory evaluation as indicated.	None	Not reviewed, Deleted	--
C	C	2	Comprehensive substance use history, including onset and pattern of progression, past sequelae and past treatment episodes (include all substances, e.g., alcohol, illicit drugs, tobacco, caffeine, over-the-counter medications, prescription medications, inhalants).	None	Not reviewed, Deleted	--

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
C	C	3	Use empathic and non-judgmental (versus confrontational) therapist style, being sensitive to gender, cultural, and ethnic differences.	None	Not reviewed, Deleted	--
C	C	4	DoD active duty members involved in an incident in which substance use is suspected to be a contributing factor are required to be referred to specialty SUD care for evaluation. Command should be contacted to discuss administrative and clinical options if the member refuses to be evaluated (see Appendix D).	None	Not reviewed, Deleted	--
C	D	1	Identify and document any co-occurring disorders (CODs) in patients with substance use disorders. ■ Psychiatric history, including symptoms and their relation to substance use, current and past diagnoses, treatments and providers ■ Infectious diseases (HIV, Hepatitis C, sexually transmitted disease) ■ Nearly all daily nicotine users are nicotine dependent. Identification and treatment of co-morbid nicotine dependence may improve recovery rates of other SUDs. For patients using nicotine offer and recommend tobacco use cessation treatment. Use the Clinical Practice Guideline: Treating Tobacco Use & Dependence: 2008 Update from the U.S. Department of Health and Human Services at http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf and the ■ VA/DoD Clinical Practice Guideline for Management of Tobacco Use ■ Medical COD that may be related to or affected by substance use (e.g., diabetes, cardiovascular disease, digestive disorders, skin infections, respiratory disorders).	None	Not reviewed, Amended	Recommendation 22

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
C	D	2	Individuals with SUD should be assessed for any significant, unmet psychosocial needs or situational stressors. If the patient is not willing to engage in any addictions focused care, provide motivational intervention and determine whether treatment for medical and psychiatric problems can be effectively and safely provided. Continue to try to engage the patient in addictions treatment (see annotation K). These include but are not limited to: ■ Inadequate or no housing ■ Financial difficulties, especially if unable to meet basic needs ■ Problematic family relationships or situations (including caregiver burden or domestic violence) ■ Poor social support ■ Religious and spiritual problems ■ Occupational problems ■ Difficulties with activities of daily living or instrumental activities of daily living ■ Any other acute or chronic situational stressors.	None	Not reviewed, Deleted	--
C	E	1	Recognize that feedback about laboratory assessments may improve patients' motivation to change and may serve as a baseline to monitor SUD treatment progress.	None	Reviewed, New-replaced	Recommendation 23
C	E	2	Review the assessment, including diagnosis, past treatment response and the patient's perspective on current problems; co-occurring disorders related to SUD; the patient's motivational level, treatment preferences and short- and long-term goals.	None	Not reviewed, Deleted	--
C	E	3	Present and discuss with the patient appropriate treatment options in a way that motivates ongoing cooperation with the provider and supports subsequent decisions about referral or brief intervention.	None	Not reviewed, Deleted	--
C	E	4	Present and discuss the treatment options with the patient and significant others.	None	Not reviewed, Deleted	--
C	E	5	Determine which treatments could be offered in general healthcare (including primary care), based on availability of a provider, severity and chronicity of the SUD, active involvement with recovery supports in the community, prior treatment response, and patient's preference and likelihood of adherence.	None	Not reviewed, Amended	Recommendation 3
C	E	6	Involve the patient in prioritizing problems to be addressed in the initial treatment plan, and in selecting specific treatment goals, regardless of the level of care selected (See Table C – 1).	None	Not reviewed, Deleted	--

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
C	E	7	If the patient is not willing to engage in any addictions focused care, provide motivational intervention and determine whether treatment for medical and psychiatric problems can be effectively and safely provided. Continue to try to engage the patient in addictions treatment (see annotation K).	None	Not reviewed, Deleted	--
C	F	1	Offer referral to specialty SUD care for addiction treatment if the patient: ■ May benefit from additional evaluation or motivational interviewing regarding his/her substance use and related problems ■ Has tried and been unable to change substance use on his/her own or does not respond to repeated brief intervention ■ Has been diagnosed with substance dependence ■ Has previously been treated for an alcohol or other substance use disorder ■ Has an AUDIT-C score of > 8.	A	Not reviewed, Amended	Recommendation 3
C	F	2	DoD active duty members involved in an incident in which substance use is suspected to be a contributing factor are required to be referred to specialty SUD care for evaluation. Command should be contacted to discuss administrative and clinical options if the member refuses to be evaluated (see Appendix D).	None	Not reviewed, Deleted	--
C	G	1	Discuss pharmacotherapy options with all patients with opioid and/or alcohol dependence.	None	Reviewed, New-replaced	Recommendation 5 Recommendation 6
C	G	2	Initiate pharmacotherapy if indicated and monitor adherence and treatment response.	None	Reviewed, New-replaced	Recommendation 5 Recommendation 6

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
C	H	1	Provide a brief intervention (counseling) for Unhealthy Alcohol Use , which includes the following components: ■ Express concern that the patient is drinking at unhealthy levels known to increase his/her risk of alcohol-related health problems ■ Provide feedback linking alcohol use and health, including: • Personalized feedback (i.e., explaining how alcohol use can interact with the patient's medical concerns [e.g., hypertension, depression/anxiety, insomnia, injury, diabetes, breast cancer risk, interactions with medications]) OR • General feedback on health risks associated with drinking. ■ Advise: • To abstain (if there are contraindications to drinking) OR • To drink below recommended limits (specified for the patient by gender, age and health status) ■ Support the patient in choosing a drinking goal, if he/she is ready to make a change.	A	Reviewed, Deleted	--
C	H	2	Provide medical management in the treatment of alcohol use disorder and consider medical management for other substance use disorders that includes: ■ Monitoring self-reported use, laboratory markers and consequences ■ Use of medication, adherence monitoring, response to treatment and adverse effects ■ Education and referral to community support for recovery (e.g., Alcoholics Anonymous).	C	Reviewed, New-replaced	Recommendation 13
C	H	3	Offer referral to a specialty addictions program when indicated.	None	Not reviewed, Amended	Recommendation 3
C	I	1	Referral to psychosocial rehabilitation services should be offered to individuals with identified, unmet psychosocial needs, regardless of the population or setting, and regardless of the type of pharmacotherapy or psychotherapy being administered.	None	Reviewed, Deleted	--

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
C	I	2	Prioritize and address other coexisting biopsychosocial problems with services targeted to these problem areas, rather than increasing intensity of addiction-focused psychosocial treatment alone. ■ Address transitional housing needs to facilitate access to treatment and promote a supportive recovery environment ■ Provide social/vocational/legal services in the most accessible setting to promote engagement and coordination of care ■ Address deferred problems as part of treatment plan updates and monitor emerging needs ■ Coordinate care with other social service providers or case managers.	B	Not reviewed, Amended	Recommendation 22
C	J	1	Prioritize and address co-occurring medical and psychiatric conditions.	None	Not reviewed, Deleted	--
C	J	2	Recommend and offer cessation treatment to patients with nicotine dependence. Use the Clinical Practice Guideline: Treating Tobacco Use & Dependence: 2008 Update from the U.S. Department of Health and Human Services at: http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf and the VA/DoD Clinical Practice Guideline for Management of Tobacco Use.	None	Not reviewed, Deleted	--
C	J	3	Treat concurrent psychiatric disorders consistent with VA/DoD clinical practice guidelines (e.g., Major Depressive Disorder, Post Traumatic Stress, Bipolar Disorder, Psychoses) including concurrent pharmacotherapy.	None	Not reviewed, Deleted	--
C	J	4	Provide multiple services in the most accessible setting to promote engagement and coordination of care.	None	Reviewed, Deleted	--
C	J	5	Monitor and address deferred problems and emerging needs through ongoing treatment plan updates.	None	Reviewed, New-replaced	Recommendation 23
C	J	6	Coordinate care with other providers.	None	Not reviewed, Amended	Recommendation 22
C	K	1	Reassess response to treatment periodically and systematically, using standardized and valid instrument(s) whenever possible. Indicators of treatment response include ongoing substance use, craving, side effects of medication, emerging symptoms, etc.	None	Reviewed, New-replaced	Recommendation 23
C	K	2	Consider obtaining biological markers of recent substance use.	None	Reviewed, New-replaced	Recommendation 23
C	K	3	Assess co-occurring medical problems associated with substance use through history, physical exam and appropriate laboratory evaluation.	None	Not reviewed, Amended	Recommendation 22

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
C	L	1	Ask the patient about any use, craving, or perceived relapse risk.	None	Reviewed, New-replaced	Recommendation 23
C	L	2	Provide feedback to patient regarding improvement or deterioration in laboratory assessments affiliated with substance use.	None	Reviewed, New-replaced	Recommendation 23
C	L	3	Encourage abstinence or reduced use, consistent with the patient's motivation and agreement	None	Not reviewed, Deleted	--
C	L	4	Convey openness to discuss any future concerns that may arise and encourage the patient to discuss them with you.	None	Not reviewed, Deleted	--
C	M	1	Discuss the patient's current use of alcohol and other drugs and address any potential problem areas, such as recent initiation of use, increase in use, and use to cope with stress.	None	Not reviewed, Deleted	--
C	M	2	Inform patient about potential age- and gender-related problems, such as: ■ Abusive drinking or other drug use in the young adult ■ Alcohol and other drug use during pregnancy ■ Medication misuse or heavy drinking in the older adult.	None	Not reviewed, Deleted	--
C	M	3	Convey openness to discuss any future concerns that may arise and encourage the patient to discuss them with you.	None	Not reviewed, Deleted	--
C	M	4	Periodically inquire about alcohol and drug use at future visits.	None	Not reviewed, Deleted	--
C	N	1	For patients who are not improving a consideration should be given to either: ■ Changing to another medication or intervention; or ■ Changing treatment intensity by: • Increasing the intensity of care, or • Increasing the dose of the medication, or • Adding a medication.	None	Reviewed, New-replaced	Recommendation 23

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
C	N	2	For patients who do not stabilize and refuse to engage in any type of ongoing care with any provider (e.g., medical, psychiatric, or addiction specialty) episodic attention to substance use may be accomplished by the following: ■ Provide crisis intervention, as needed ■ At any contact initiated by the patient: • Assess current substance use • Recommend that the patient accept ongoing care in the most appropriate setting • Designate a single provider to coordinate care for patients who repeatedly present in crisis • Consider involving supportive family members or significant others, if the patient agrees. For DoD active duty members this may include first line supervisor when appropriate, and will necessarily include the unit commander • Initiate involuntary treatment procedures, if imminent threat to safety occurs (e.g., suicidal, violent, or unable to care for self). ■ Continue to reinforce and endorse increased appropriate engagement and adherence.	None	Not reviewed, deleted	--
C	N	3	Consider consultation with mental health or SUD specialty.	None	Not reviewed, Amended	Recommendation 3
P	B	1	Assess opioid dependence using DSM-IV-TR criteria.	None	Not reviewed, Deleted	--
P	C	1	Provide access to opioid agonist treatment (OAT) for all opioid dependent patients, under appropriate medical supervision and with concurrent addiction-focused psychosocial treatment as indicated.	A	Reviewed, New-replaced	Recommendation 8 Recommendation 13
P	C	2	Strongly recommend methadone or sublingual buprenorphine/naloxone maintenance as first line treatments due to their documented efficacy in improving retention and reducing illicit opioid use and craving.	A	Reviewed, New-replaced	Recommendation 8
P	C	3	Note: In pregnancy, buprenorphine monotherapy is preferred.	None	Not reviewed, Deleted	--
P	D	1	Individualize the choice of setting based on patient characteristics and availability of facilities to treat patients with opioid agonist therapy (OAT).	None	Reviewed, New-replaced	Recommendation 10

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
P	D	2	Appropriate psychosocial interventions should be provided as part of the opioid agonist therapy (OAT).	A	Reviewed, New-replaced	Recommendation 14 Recommendation 15 Recommendation 16
P	E	1	Opioid Agonist Treatment Program (OATP) and office-based opioid treatment (OBOT) must be provided in the context of a complete treatment program that includes: ■ Appropriate adjustment of opioid agonist doses to maintain a therapeutic range between signs/symptoms of overmedication (e.g., somnolence, miosis, itching, hypotension, and flushing) and opioid withdrawal (e.g., drug craving, anxiety, dysphoria, and irritability) • Usual dosage range for optimal effects: 60–120 mg/day • Buprenorphine target dose is generally up to 16 mg daily; doses above 32 mg are rarely indicated. In all cases, except pregnancy, the combination product of buprenorphine/naloxone should be used. ■ Relapse monitoring to promote effective outcomes ■ Adequate frequency of toxicology for alcohol and other drugs of abuse. Drug testing for both methadone and buprenorphine should also be considered to ensure compliance with the prescription and for detection of possible diversion ■ Appropriate psychosocial interventions.	A (for specific portion of the rec)	Reviewed, New-replaced	Recommendation 13
P	F	1	Consider monitored administration of naltrexone maintenance in highly motivated opioid dependent patients. See Table P-3.	C	Not reviewed, Deleted	--
P	F	2	Consider opioid agonist treatment (OAT) or long-term therapeutic community before naltrexone as first line approaches for chronic opioid dependent patients	None	Not reviewed, Deleted	--
P	G	1	Prior to starting naltrexone, ensure that the patient is opioid-free as naltrexone is an opioid antagonist and may precipitate withdrawal.	None	Not reviewed, Deleted	--
P	G	2	Consider pharmacologically assisted withdrawal (See Module S: Stabilization and Withdrawal Management, Annotation F), unless the patient successfully completed a naloxone challenge and/or has had at least 7-10 days of verified abstinence.	None	Not reviewed, Deleted	--
P	H	1	Provide appropriate dosing, treatment retention- and adherence-enhancing techniques, and relapse monitoring to promote effective outcomes.	None	Not reviewed, Deleted	--
P	H	2	Carefully start oral naltrexone at a dose of 25 mg once daily. If no signs of withdrawal occur, the dose may be increased to 50 mg daily on the following day. Extended dosing intervals, using equivalent weekly doses, may be used for supervised administration (see Table P-4).	None	Not reviewed, Deleted	--

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
P	I	1	Identify patients with alcohol dependence that should be considered for addiction-focused pharmacotherapy.	None	Not reviewed, Deleted	--
P	J	1	Routinely consider oral naltrexone, an opioid antagonist, and/or acamprosate for patients with alcohol dependence. Note that in VA, acamprosate is currently a non-formulary medication with criteria for use posted at http://vaww.national.cmop.va.gov/PBM/Clinical%20Guidance/Forms/AllItems.aspx	A	Reviewed, New-replaced	Recommendation 5 Recommendation 6
P	J	2	Medications should be offered in combined with addiction-focused counseling.	A	Reviewed, New-replaced	Recommendation 5 Recommendation 6
P	J	3	Injectable naltrexone should be considered when medication adherence is a significant concern in treating alcohol dependence and should be combined with addiction-focused counseling. Note that in VA, injectable naltrexone is currently a non-formulary medication with criteria for use posted at http://vaww.national.cmop.va.gov/PBM/Clinical%20Guidance/Forms/AllItems.aspx	A	Reviewed, New-replaced	Recommendation 5 Recommendation 6
P	J	4	If patient does not respond to one of the approved medications, a trial on one of the other approved medications is warranted.	None	Reviewed, Deleted	--
P	J	5	Because of the risk of significant toxicity and limited evidence of effectiveness, risk and benefits of disulfiram should be considered and disulfiram should only be used when abstinence is the goal and when combined with addiction-focused counseling. The informed consent discussion with the patient should be documented.	B	Reviewed, Deleted	--
P	J	6	Dosing of these pharmacotherapies should be consistent with medication trials and recommendations in appropriate drug references (see Table P-5).	None	Reviewed, Deleted	--
S	B	1	Interview the patient and other collateral informants, where appropriate, about medical and mental health history and use of prescription and non-prescription medications before initiating extensive diagnostic testing.	None	Not reviewed, Deleted	--
S	B	2	Note any history of recent head trauma.	None	Not reviewed, Deleted	--
S	B	3	Order laboratory tests selectively, aiming to detect potential medical causes for the presenting symptoms, where indicated by: ■ Specific symptoms found on the medical review of systems ■ Evidence of unusual symptom profiles ■ History of atypical illness course ■ Abnormal screen for cognitive status, particularly in the elderly patient.	None	Not reviewed, Deleted	--

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
S	C	1	Refer patients with problems that require emergency care or urgent action to emergency care for further action as needed.	None	Not reviewed, Deleted	--
S	D	1	Assure the patient's immediate safety and determine the most appropriate setting.	None	Reviewed, Deleted	--
S	D	2	Refer for mental health treatment or assure that follow-up appointment is made.	None	Not reviewed, Amended	Recommendation 3
S	D	3	Inform and involve someone close to the patient.	None	Not reviewed, Deleted	--
S	D	4	Limit access to means of suicide.	None	Not reviewed, Deleted	--
S	D	5	Increase contact and make a commitment to help the patient through the crisis.	None	Not reviewed, Deleted	--
S	D	6	For comatose patients, maintain airway and adequate ventilation in order to preserve respiration and cardiovascular function.	None	Not reviewed, Deleted	--
S	D	7	Emergency procedures should be considered, including the use of gastric lavage for sedative, hypnotic, and/or opioid intoxication.	None	Not reviewed, Deleted	--
S	D	8	Emergency pharmacologic interventions should be utilized as appropriate, including the use of intravenous naloxone hydrochloride for opioid overdose and flumazenil for benzodiazepine overdose.	None	Not reviewed, Deleted	--
S	D	9	Agitation secondary to intoxication from a variety of substances is best initially managed through interpersonal approaches and decreasing sensory stimuli rather than additional medications. If chemotherapeutic agents are necessary, the short acting IM benzodiazepines (e.g., lorazepam) and high potency neuroleptics should be considered For DoD active duty members: follow DoD and Service-specific policies, as mental health/emergency referral is likely mandated.	None	Not reviewed, Deleted	--

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
S	E	1	Obtain and document necessary information to classify level of withdrawal and factors that may influence the severity of the withdrawal (see Appendix B-6 for a list of withdrawal signs and symptoms for the different types of substances): ■ Determine type of substance of use ■ Determine time since last use ■ Determine concurrent use of other substances or prescriptions ■ Determine co-occurring medical and/or psychiatric disorders ■ Consider past withdrawal experiences.	None	Not reviewed, Deleted	--
S	E	2	Use laboratory results and patient observation to determine the level of tolerance (e.g., high blood level in patient who appears to be not intoxicated).	None	Not reviewed, Deleted	--
S	E	3	Use standardized measures to assess the severity of withdrawal symptoms such as CIWA-Ar (see Box S-1) or COWS (see Box S-2).	B	Not reviewed, Amended	Recommendation 26
S	E	4	Evaluate patients using multiple substances (e.g., opioids and sedative-hypnotics) for risk of withdrawal from each substance.	None	Not reviewed, Amended	Recommendation 27
S	F	1	Indications for withdrawal management from alcohol or sedative-hypnotics ■ Patient with alcohol dependence with observed withdrawal symptoms ■ CIWA-Ar score for at least mild withdrawal (>10) ■ Patients with dependence on central nervous system depressants, due to the risks of untreated withdrawal in severely dependent persons.	None	Not reviewed, Deleted	--
S	F	2	Relative contraindication for medically supervised withdrawal management from alcohol ■ Patients with minimal withdrawal symptoms that are not accompanied by complicating co-occurring disorders. Such patients may respond sufficiently to generalized support, reassurance, and frequent monitoring.	None	Not reviewed, Deleted	--
S	F	3	Potential indications for medically supervised opioid withdrawal: ■ Patient with physical dependence in the absence of clinical indications for ongoing treatment (e.g., severe pain disorder) ■ Patient with physical dependence accompanied by aberrant or non-adherent behavior (e.g., obtaining prescriptions from multiple providers, escalating doses without provider consultation, or buying medications on the street) ■ Agreement to provide naltrexone for treatment of opioid dependence ■ Patient who does not request or want opioid agonist medical therapy but wants non-pharmacologic treatment for opioid dependence.	None	Reviewed, Deleted	--

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
S	F	4	Contraindication for opioid withdrawal management: ■ Chronic severe opioid dependence. For such patients, first line therapy is methadone or sublingual buprenorphine/naloxone maintenance treatment (See Module P - Addiction Focused Pharmacotherapy) ■ Two or more unsuccessful medically supervised withdrawal episodes within a 12-month period. Such patients should be assessed for opioid agonist therapy.	None	Reviewed, Deleted	--
S	F	5	Consider using a structured assessment tool to evaluate and track behaviors suggestive of addiction, such as inappropriate medication use, and to increase the provider's confidence in determinations of appropriate vs. inappropriate opioid use.	None	Reviewed, Deleted	--
S	F	6	Evaluate opioid dependent patients for severe acute or chronic physical pain that may require appropriate short-acting opioid agonist medication in addition to the medication needed to prevent opioid withdrawal symptoms (see also VA/DoD Clinical Practice Guideline for Management of Chronic Opioid Therapy at: http://www.healthquality.va.gov).	None	Reviewed, Deleted	--
S	G	1	Consider the following indications for inpatient medically supervised withdrawal: ■ Current symptoms of at least mild alcohol withdrawal (e.g., CIWA-Ar score ³10) ■ History of delirium tremens or withdrawal seizures ■ Inability to tolerate oral medication ■ Imminent risk of harm to self or others ■ Recurrent unsuccessful attempts at ambulatory medically supervised withdrawal ■ Reasonable likelihood that the patient will not complete ambulatory medically supervised withdrawal (e.g., due to homelessness) ■ Active psychosis or severe cognitive impairment ■ Chronic liver disease or cardiovascular disease, pregnancy, or lack of medical support system.	C	Reviewed, Amended	Recommendation 27 Recommendation 28
S	H (1)	1	Use either of the following two acceptable pharmacotherapy strategies for managing alcohol withdrawal symptoms: ■ Symptom-triggered therapy where patients are given medication only when signs or symptoms of withdrawal appear (e.g., PRN dosing) ■ A predetermined fixed medication dose with gradual tapering over several days may be considered for some patients, although it is inferior to symptom-triggered therapy.	A, B	Not reviewed, Amended	Recommendation 29
S	H (1)	2	Repeat standardized assessments, such as the CIWA-Ar scale for alcohol withdrawal, to guide dosing decisions (e.g., if and when to dose) until stabilized.	None	Reviewed, New-replaced	Recommendation 23

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
S	H (1)	3	Consider the following procedures for monitoring ambulatory alcohol withdrawal as safe and effective alternatives to inpatient approaches: ■ Medical or nursing staff should assess the patient in person, either daily or every other day (patient contact may be made by telephone on other days), to include: • Patient report of any alcohol use the previous day • Reported medication intake compared to the medication dispensed the previous day • Tremor, restlessness, and previous night's sleep • Skin (e.g., color and turgor). ■ Urine toxicology or a breathalyzer test of blood alcohol content should be completed. ■ If the daily screening is positive for any one of the following, the patient should be medically evaluated before initiating or continuing outpatient withdrawal management, or hospital admission should be considered: • Blood sugar≥400 or positive anion gap • History of recent hematemesis, melena, or other gastrointestinal bleeding disorder • Bilirubin ≥ 3.0 • Creatinine ≥ 2.0 • Systolic blood pressure ≥ 180 or diastolic blood pressure ≥ 110 • Unstable angina • Temperature ≥ 101 degrees • BAC ≥ 0.08 on two outpatient visits.	None	Not reviewed, Deleted	--
S	H (1)	4	For inpatient treatment of alcohol withdrawal, use benzodiazepines over non-benzodiazepine sedative-hypnotics because of documented efficacy, and a greater margin of safety. Benzodiazepines are the drug of choice in this setting, given adequate monitoring, because they reduce withdrawal severity, incidence of delirium, and seizures. All benzodiazepines appear to be effective, but agents without active metabolites such as lorazepam or oxazepam may be preferred in patients with liver impairment.	A	Reviewed, Amended	Recommendation 30
S	H (1)	5	Dose and withdrawal scales should be individualized for each patient. Geriatric patients should start with lower doses of benzodiazepines than younger adults.	A	Not reviewed, Deleted	--
S	H (1)	6	For managing mild to moderate alcohol withdrawal, carbamazepine and valproic acid can be used as an effective supplement or alternative to benzodiazepines. They may be considered in patients that cannot use benzodiazepines (e.g., abuse liability or allergy/adverse reactions).	B	Reviewed, New-replaced	Recommendation 31

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
S	H (1)	7	Other agents, such as beta-blockers, and clonidine, are generally not considered as appropriate monotherapy for alcohol withdrawal, but may be considered in conjunction with benzodiazepines in certain patients.	C	Not reviewed, Deleted	--
S	H (1)	8	During and after medically supervised withdrawal, emphasis should be placed on engagement in ongoing addiction treatment.	C	Not reviewed, Deleted	--
S	H (1)	9	Use of alcohol as an agent for medically supervised withdrawal is contraindicated.	D	Not reviewed, Amended	Recommendation 32
S	H (2)	1	Substitute phenobarbital for the addicting agent and taper gradually. ■ The average daily sedative-hypnotic dose is converted to a phenobarbital equivalent and divided into 3 doses per day for 2 days (see Appendix E for phenobarbital equivalencies for sedative hypnotics). ■ Phenobarbital dose should be reduced by 30 mg per day, beginning on day 3.	A	Not reviewed, Amended	Recommendation 36
S	H (2)	2	Substitution then tapering: For patients on a shorter acting benzodiazepine, substitute a longer acting benzodiazepine at an equivalent dose (e.g., chlordiazepoxide) and taper 10 percent per day, over 1 to 2 weeks.	None	Not reviewed, Amended	Recommendation 36
S	H (2)	3	Simple tapering: Gradually decrease the dosage of the long-acting substance the patient is currently taking.	None	Not reviewed, Amended	Recommendation 36
S	H (2)	1	Medically supervised opioid withdrawal is rarely effective as a long-term strategy for treatment of opioid dependence because of high relapse rates. Opioid maintenance with buprenorphine/naloxone or methadone is the definitive treatment of choice in most cases.	B	Reviewed, New-replaced	Recommendation 33
S	H (3)	2	If pursuing medically supervised opioid withdrawal, the preferred approaches are initial stabilization and subsequent short or extended taper with opioid agonist therapy.	None	Reviewed, New-replaced	Recommendation 34
S	H (3)	3	Set the length of the taper period based on the treatment setting and severity of the dependence.	None	Not reviewed, Deleted	--
S	H (3)	4	Medically supervised withdrawal can usually be accomplished in 4 to 7 days in an inpatient setting, to quickly achieve opioid abstinence prior to treatment in a drug-free setting, preferably with initiation of naltrexone.	None	Not reviewed, Deleted	--

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
S	H (3)	5	Withdrawal using buprenorphine/naloxone: ■ Only physicians with a waiver from the US Department of Health and Human Services can prescribe buprenorphine/naloxone ■ Initial stabilization is accomplished via induction with buprenorphine/naloxone just as it would be for maintenance with this agent (See Table S-1). To reduce the risk of precipitated withdrawal, the patient must be in sufficient opioid withdrawal to be manifesting objective signs of withdrawal prior to starting buprenorphine/naloxone usually at least 8 hours since the patient's last use of heroin or other short-acting opioid or at least 24 and preferably at least 48 hours have elapsed since the last use of methadone or other long-acting opioid ■ Within 1-3 days, a daily dose of buprenorphine/naloxone should be achieved that eliminates signs and symptoms of opioid withdrawal, suppresses opioid craving, and eliminates illicit opioid use. This dose could range from 2/0.5 mg per day to 16/4 mg per day and would rarely exceed that amount ■ Once stabilization has been achieved the dose can be rapidly tapered over 5-7 days. There is little evidence that prolonging the taper leads to better results. (If the patient and physician prefer a longer taper, there is also no evidence that a longer taper is harmful).	None	Not reviewed, Deleted	--

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
S	H (3)	6	Withdrawal using methadone: ■ Withdrawal using methadone can only be performed in the context of a federally licensed opioid treatment program where daily medication dispensing can occur. For patients not engaged in methadone maintenance through an opioid treatment program, withdrawal should be managed with buprenorphine ■ Initial stabilization is accomplished via induction with methadone just as it would be for maintenance with this agent. Withdrawal signs do not have to be observed prior to starting methadone, but with methadone there is risk of medication accumulation, toxicity, and overdose. Initial dosing should be very conservative with careful daily observation of the patient. Initial daily doses can range from 5 mg to a maximum of 30 mg ■ Within days to weeks, a daily dose of methadone should be achieved that eliminates signs and symptoms of opioid withdrawal, suppresses opioid craving, and eliminates illicit opioid use. This dose could range from 30 mg per day to doses as high as 120 mg per day ■ Once stabilization has been achieved, the dose can be gradually tapered over a period of weeks to months. Dose decreases of more than 5 -10 mg/day of methadone are generally poorly tolerated. In contrast to the evidence with buprenorphine/naloxone, with methadone, longer taper periods should be used in the outpatient setting to minimize patient discomfort and maximize chances of success A period of two to three weeks is generally sufficient for short-term outpatient medically supervised withdrawal in the most stable and motivated individual. The higher the stabilization dose, the longer the taper is likely to take. The taper should proceed more gradually as the dose becomes lower.	None	Not reviewed, Deleted	--
S	H (3)	7	The 180-day stabilization/medically supervised withdrawal regimen should be considered to facilitate work on patients' early recovery problems, while stabilized on sublingual buprenorphine or a relatively low dose (50-60 mg/day) of methadone. Stabilization is followed by short-term medically supervised withdrawal from buprenorphine or methadone and transition to a drug-free rehabilitation program.	None	Not reviewed, Deleted	--
S	H (3)	8	Clonidine, an alpha-adrenergic agonist, can be considered as an adjunctive agent for symptom relief during inpatient medically supervised opioid withdrawal; however, outpatient success is much lower. If using clonidine, adjunctive medications for anxiety, restlessness, insomnia, muscle aches, nausea, and diarrhea can also be prescribed.	None	Reviewed, New-replaced	Recommendation 35
S	I	1	Identify patients in need of additional withdrawal management or stabilization before proceeding with further evaluation or treatment	None	Not reviewed, Deleted	--

2009 Module[1]	2009 Section	2009 Number	2009 Recommendation Text[2]	2009 Grade[3]	Category[4]	2015 Recommendation[5]
S	I	2	Medically supervised withdrawal is successful to the degree that the patient: ■ Is physiologically stable ■ Avoids hazardous medical consequences of withdrawal ■ Experiences minimal discomfort ■ Reports being treated with respect ■ Completes the medically supervised withdrawal protocol (e.g., no longer requires medication for withdrawal symptom management).	None	Not reviewed, Deleted	--
S	J	1	If medically supervised withdrawal is unsuccessful, or treatment engagement is not achieved, consider one of the following: ■ A more intensive level of care for withdrawal management (e.g., inpatient) ■ Identify patients who can benefit from implementation of a care management plan, if acceptable to the patient (see Module C, Annotation K).	None	Not reviewed, Deleted	--

Appendix F: Participant List

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Appendix G: Conflict of Interest Disclosures Based on Financial Relationships with Industry

Work Group Member	Disclosed Conflict of Interest
Andrew Saxon, MD	Received royalties from UpToDate; organizations supplied study medications (Alkermes provided extended release naltrexone; Reckitt Benckiser provided Suboxone)

Appendix H: Literature Review Search Terms and Strategy

A. Topic-specific Search Terms

The search strategies employed combinations of free-text keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. Strategies for each bibliographic database follow this table.

Table H-1. EMTREE, Medical Subject Headings (MeSH), PsycInfo, and Keywords

Concept	Controlled Vocabulary	Keywords
General Substance Abuse	**EMBASE (EMTREE)** 'substance abuse'/exp 'inhalant abuse'/exp 'intravenous drug abuse'/exp 'multiple drug abuse'/exp 'drug dependence'/exp 'withdrawal syndrome'/exp addiction/mj 'drug abuse'/exp **MEDLINE (MESH)** exp substance-related disorders/ exp substance withdrawal syndrome/ exp drug overdose/ substance abuse, intravenous/ **PsycINFO** exp drug abuse/ exp drug dependency/ exp polydrug abuse/ addiction/ exp drug addiction/	drug(s) substance polydrug AND abuse addict(s) addiction(s) disorder(s) misuse user(s)
AUD	**EMBASE (EMTREE)** 'Alcohol abuse'/exp 'alcohol use disorder'/exp alcoholism/exp 'drinking behavior'/exp 'alcohol abstinence'/exp 'alcohol withdrawal'/exp **MEDLINE (MESH)** exp alcohol-related disorders/ exp alcohol drinking/ exp alcoholics/ **PsycINFO** exp alcohol abuse/ exp alcoholism/ exp alcohol intoxication/ alcohol withdrawal/	alcohol abuse alcohol misuse alcohol intoxication alcohol addiction alcoholics alcoholism drunk drunken

Concept	Controlled Vocabulary	Keywords		
Opioids and Opioid Use Disorder	**EMBASE (EMTREE)** 'opiate addiction'/exp 'analgesic agent abuse'/exp 'narcotic dependence'/exp ('narcotic analgesic agent'/exp **MEDLINE (MeSH)** exp opioid-related disorders/ exp Analgesics, Opioid/ exp narcotics/ **PsycINFO** exp opiates/ exp analgesic drugs/ exp narcotic drugs/	analgesic codeine heroin hydrocodone methadone morphine narcotics opiates opioids oxycodone oxycontin percocet vicodin	AND	abuse addict(s) addiction(s) disorder(s) misuse user(s)
Other Substances (cannabis, stimulants, hypnotic sedatives)	**EMBASE (EMTREE)** 'cannabis'/exp 'cannabis addiction'/exp 'cocaine'/exp 'cocaine dependence'/exp 'cannabis use'/exp 'central stimulant agent'/exp 'amphetamine'/exp 'methamphetamine'/exp 'dexamphetamine'/exp 'hypnotic sedative agent'/exp 'sedative agent'/exp 'barbituric acid derivative'/exp 'benzodiazepine derivative'/exp **MEDLINE (MeSH)** exp amphetamine-related disorders/ exp cocaine-related disorders/ exp marijuana abuse/ exp opioid-related disorders/ exp inhalant abuse/ exp phencyclidine abuse/ OR exp "hypnotics and sedatives"/ exp barbiturates/ exp benzodiazepines/ **PsycINFO** Exp amphetamine/ exp barbiturates/ exp benzodiazepines/ exp cocaine/ exp crack cocaine/ exp inhalant abuse/ exp sedatives/ exp hypnotic drugs/	Adderall Ambien amphetamine(s) amytal Ativan barbiturate(s) barbs benzodiazepine(s) butalbital cannabis cocaine dextroamphetamine Dexedrine diethylamide downers eszopiclone Fiorinal Halcion hypnotic(s) inhalant(s) ketamine librium LSD lysergic acid lunesta marijuana "meth" methamphetamine nembutal PCP phencyclidine phenobarbital roofies	AND	abuse addict(s) addiction(s) disorder(s) misuse user(s)

Concept	Controlled Vocabulary	Keywords
	exp marijuana/ exp marijuana usage/	roofinol salvia sedative(s) seconal sonata stimulant(s) uppers Valium Xanax Zaleplon Zolpidem
Pharmacologic Treatments (General)	**EMBASE (EMTREE)** 'drug therapy'/exp drug therapy/lnk [floating subheading] 'drug combination'/exp 'drug combination'/lnk 'drugs used in the treatment of addiction'/exp 'drug administration'/exp 'drug administration'/lnk 'drug comparison'/exp 'drug comparison'/lnk **MEDLINE (MESH)** exp drug therapy/ drug therapy [Floating Subheading] **PsycINFO** exp drug therapy/	medicine(s) medication(s) pharmacotherapeutic pharmacotherapy pharmacotherapies
Pharmacologic Treatments (specific drug classes and drugs)	**EMBASE (EMTREE)** 'opiate agonist'/exp 'opiate receptor affecting agent'/exp 'alpha adrenergic receptor stimulating agent'/exp 'opiate antagonist'/exp **MEDLINE(MESH)** exp adrenergic agents/ exp adrenergic agonists/ exp adrenergic antagonists/ exp dopamine agonists/ **PsycINFO** exp narcotic antagonists/ exp narcotic agonists/ exp narcotic antagonists/ exp adrenergic receptors/ exp dopamine agonists/ exp serotonin agonists/ exp benzodiazepine agonists/	alcophobin acamprosate antabus Antabuse anticol agonist(s) atomoxetine baclofen buprenorphine bupropion buspirone citalopram clonidine desipramine dicupral disulfiram divalproex dronabinol esperal fluoxetine

Concept	Controlled Vocabulary	Keywords
		fluvoxamine gabapentin guanfacine guanabenz imipramine LAAM Levomethadyl acetate lofexidine methadone modafinil nalmefene naloxone naltrexone narcotic agonist(s) narcotic antagonist(s) nefazodone odansetron olanzapine opiate agonist(s) opiate antagonist(s) paroxetine quetiapine Revia sertraline tetrahydrocannabinol teturam Topamax topiramate Topimax valproic acid varenicline
Psychosocial Treatments	**EMBASE (EMTREE)** psychotherapy/exp 'cognitive therapy'/exp counseling/exp 'Acceptance and commitment therapy'/exp 'support group'/exp 'motivational interviewing'/exp 'alcohol rehabilitation program'/exp 'alcoholics anonymous'/exp 'community based rehabilitation'/exp **MEDLINE (MeSH)** exp psychotherapy/ exp psychotherapy, brief/ exp psychology, applied/ exp counseling/ exp self-help groups/ exp group psychotherapy/	"alcohol sbi" community reinforcement community help/group/support contingency management counseling cognitive therapy/counseling couples therapy/counseling group therapy/counseling motivational interview(ing) mutual help/group/support psychosocial therapy/counseling psychotherapy psychotherapies psychotherapeutic behavioral therapy/counseling motivational therapy/counseling support group

Concept	Controlled Vocabulary	Keywords
	PsycINFO exp psychotherapy/ exp cognitive therapy/ exp couples therapy/ exp marriage counseling/ exp family therapy/ exp psychotherapeutic processes/ exp psychotherapeutic techniques/ exp Alcoholics anonymous/ psychosocial rehabilitation/ exp drug rehabilitation/ exp alcohol rehabilitation/ exp motivational interviewing/	twelve step 12-step brief / short / concise / abrupt / time limited **AND** advice / advisory / counsel(ing) / intervention(s) / motivate / motivational / psychotherapy / psychotherapies / psychotherapeutic therapy / therapies / treatment*
Settings and Treatment Intensity	**EMBASE (EMTREE)** 'alcohol rehabilitation program'/exp 'rehabilitation'/de 'secondary health care'/exp 'health care facility'/de 'community mental health center'/exp 'health center'/exp 'mental health center'/exp 'rehabilitation center'/exp 'residential home'/exp 'secondary care center'/exp 'tertiary care center'/exp 'patient referral'/exp 'primary health care'/exp 'general practitioner'/exp **MEDLINE (MeSH)** exp Substance Abuse Treatment Centers/ health facilities/ exp community health centers/ exp community mental health centers/ exp outpatient clinics, hospital/ exp secondary care centers/ exp tertiary care centers/ exp residential facilities/ exp primary health care/ exp "Referral and Consultation"/ exp "delivery of healthcare"/ **PsycINFO** exp Community Mental Health Services/ exp Mental Health Services/ exp Health Care Services/ exp Treatment Facilities/	ambulatory center(s) clinic* facility facilities family physician(s) family practice(s)/practitioner(s) general practice(s)/practitioner(s) health center(s) health centre(s) inpatient office outpatient primary care primary health refer referral referred rehab* "secondary care" setting specialist(s) specialty "tertiary care" treatment/care setting(s)*

Concept	Controlled Vocabulary	Keywords
	exp Psychiatric Hospitals/ exp Community Mental Health Centers/ exp clinics/ exp psychiatric clinics/ exp walk in clinics/ exp Therapeutic Environment/ health care services/ exp "continuum of care"/ exp long term care/ exp mental health services/ exp primary health care/ exp mental health programs/ exp rehabilitation/ exp general practitioners/	
Patient selection/criteria	**EMBASE(EMTREE)** 'patient selection'/exp 'disease management'/exp 'practice guideline'/exp 'patient care planning'/exp **MEDLINE (MeSH)** Exp patient selection/ exp disease management/ exp Guideline Adherence/ exp Guideline/ exp Practice Guideline/ **PsycINFO** exp Treatment Guidelines/ exp Evaluation Criteria/ exp client characteristics/	patient criteria patient characteristics patient selection
Intensity of Care		aggressive intense intensive intensity level of care Levels of care long term short term
Measurement Based Care	**EMBASE (EMTREE)** 'self report'/exp 'psychological rating scale'/exp 'questionnaire'/exp 'biological marker'/exp parameters/de 'patient monitoring'/de 'named inventories, questionnaires and rating scales'/exp 'self monitoring'/exp 'Patient Health Questionnaire'/exp	"addiction severity index" assessment assess biomarker(s) brief addiction monitor continuous assessment continuous monitoring biological measure(s) instrument(s) index

Concept	Controlled Vocabulary	Keywords
	MEDLINE (MeSH) exp self report/ exp questionnaires/ exp biological markers/ exp monitoring, physiologic/ exp psychiatric status rating scales/ exp psychological tests/ exp psychometrics/ exp health status indicators/ exp "severity of illness index"/ **PsycINFO** exp measurement/ exp test scores/ exp testing methods/ exp monitoring/	Measurement based care measure(s) monitor(s) patient health questionnaire PHQ questionnaire(s) scale(s)

B. Search Strategies

Table H-2. MEDLINE/PSYCINFO (presented in OVID syntax)

Set Number	Concept	Search Statement
1	AUD	exp Alcohol-Related Disorders/ OR exp Alcohol Drinking/ OR exp Alcoholics/exp OR alcohol abuse/ OR exp alcoholism/ OR exp alcohol intoxication/ OR alcohol withdrawal/ OR alcoholism.ti,ab. OR (alcohol AND (abuse OR misuse OR intoxicat* OR addict*)).ti,ab. OR alcoholics.ti,ab. OR drunk.ti,ab. OR drunken.ti,ab.
2	OUD	exp opioid-related disorders/ OR ((exp substance-related disorders/ OR exp substance withdrawal syndrome/ OR exp drug abuse/ or exp drug dependency/ or exp polydrug abuse/ or addiction/ or exp drug addiction/ OR exp drug withdrawal/) AND (exp Analgesics, Opioid/ OR exp opiates/ OR exp analgesic drugs/ OR exp narcotics/ OR exp analgesics, opioid/OR exp narcotic drugs/)) OR ((opiate* OR opiod* OR narcotic* OR hydrocodone OR vicodin OR oxycodone OR oxycontin OR percocet OR heroin OR methadone OR morphine OR codeine OR analgesic*) AND (abuse OR addict* OR withdrawal OR disorder*)).ti,ab.
3	Cannabis, cocaine, and stimulant use disorder	exp marijuana abuse/ OR exp amphetamine-related disorders/ OR exp Cocaine-Related Disorders/ OR ((exp substance-related disorders/ OR exp substance withdrawal syndrome/ OR exp drug abuse/ or exp drug dependency/ or exp polydrug abuse/ or addiction/ or exp drug addiction/ OR exp drug withdrawal/) AND (exp Cannabis/ OR exp Amphetamine/ OR exp Cocaine/ or exp Crack Cocaine/ OR exp Marijuana/ OR exp marijuana usage/ exp OR Central Nervous System Stimulants/ OR exp CNS Stimulating Drugs/)) OR ((amphetamine* OR cocaine OR methamphetamine OR dextroamphetamine OR Dexedrine OR Adderall OR marijuana OR cannabis OR stimulant* OR "meth") ADJ3 (abuse OR misuse OR addict* OR disorder* OR user OR users)).ti,ab.

Set Number	Concept	Search Statement
4	Sedative hypnotic use disorder	(exp "Hypnotics and Sedatives"/ OR exp sedatives/ OR exp hypnotic drugs/ OR exp Barbiturates/ OR exp Benzodiazepines/) AND (*substance related disorders/ OR substance abuse, intravenous/ or exp substance withdrawal syndrome/ OR exp drug abuse/ or exp drug dependency/ or exp addiction/ or exp drug addiction/) OR ((Hypnotic* OR sedative* OR Benzodiazepine* OR barbiturate* OR Barbiturates OR Butalbital OR Firoina OR Amytal OR Nembutal OR Seconal OR uppers OR Phenobarbital OR barbs OR Ativan OR Halcion OR Librium OR Valium OR Xanax OR downers OR Ambien OR zolpidem OR Sonata OR zaleplon OR Lunesta OR eszopiclone OR roofies OR roofinol) ADJ3 (abuse OR misuse OR addict* OR disorder* OR user OR users)).ti,ab.
5	General substance abuse terms	*substance related disorders/ or exp drug overdose/ or substance abuse, intravenous/ or exp substance withdrawal syndrome/ OR exp inhalant abuse/ OR exp drug abuse/ or exp alcohol abuse/ or exp drug dependency/ or exp polydrug abuse/ or exp addiction/ or exp drug abstinence/ or exp drug addiction/ OR ((substance OR substances OR drug OR drugs OR polydrug*) ADJ3 (abuse OR misuse OR addict* OR disorder* OR user OR users)).ti,ab.
6	Pharmacotherapy (broad terms)	Exp drug therapy/ OR dt.fs. OR pharmacotherap*.ti. OR medicine*.ti. OR medication*.ti.
7	Pharmacotherapy (drug terms-alcohol use)	acamprosate OR disulfiram OR naltrexone OR atomoxetine OR baclofen OR buspirone OR citalopram OR desipramine OR fluoxetine OR fluvoxamine OR gabapentin OR imipramine OR nalmefene OR olanzapine OR ondansetron OR paroxetine OR quetiapine OR sertraline OR topiramate OR valproic acid OR varenicline
8	Pharmacotherapy (drug terms-opioid use)	exp adrenergic agents/ or exp adrenergic agonists/ or exp adrenergic antagonists/OR exp Narcotic Antagonists/ OR exp narcotic agonists/ OR exp narcotic antagonists/ OR exp adrenergic receptors/ OR buprenorphine OR naloxone OR methadone OR naltrexone OR revia OR "LAAM" OR 'levomethadyl acetate' OR clonidine OR lofexidine OR guanfacine OR guanabenz OR (alpha ADJ3 adrenergic) OR ((narcotic* OR opiate OR opioid) AND (agonist* OR antagonist*))
9	Pharmacotherapy (drug terms-cannabis/stimulant/cocaine use)	Bupropion OR divalproex OR nefazodone OR tetrahydrocannabinol OR lofexidine OR dronabinol OR modafinil OR baclofen OR exp adrenergic agonists/ OR exp narcotic agonists/ OR exp Dopamine Agonists/ or exp Serotonin Agonists/ or exp Benzodiazepine Agonists/ or exp Narcotic Agonists/OR Exp disulfiram/ OR disulfiram OR esperal OR dicupral OR disulfide OR alcophobin OR anticol OR Antabuse OR antabus OR teturam OR Topiramate OR topamax OR topimax OR agonist OR agonists
10	Psychosocial Therapies	exp psychotherapy/ OR exp psychology, applied/ OR exp Counseling/ OR exp self-help groups/ OR exp group psychotherapy/ OR exp psychotherapy/ or exp cognitive therapy/ or exp couples therapy/ or exp marriage counseling/ or exp family therapy/ OR exp psychotherapeutic processes/ or exp psychotherapeutic techniques/ exp OR Alcoholics anonymous/ OR psychosocial rehabilitation/ or exp drug rehabilitation/ OR exp alcohol rehabilitation/ OR exp motivational interviewing/ OR psychotherap*.ti,ab. OR counseling OR ((cognitive OR behavioral OR motivational OR couples OR family OR group OR psychosocial) AND

Set Number	Concept	Search Statement
		(counseling OR therapy)).ti,ab. OR "community reinforcement" OR "contingency management" OR (motivation* ADJ2 interview*) OR (twelve ADJ1 step) OR "alcoholics anonymous" OR "narcotics anonymous" OR "self help" OR ((mutual OR community) ADJ1 (help OR group* OR support)).ti,ab. OR (support ADJ1 group*).ti,ab. OR "12-step"
11	Brief interventions for alcohol use	exp Psychotherapy, Brief/ OR (brief OR short OR concise OR abrupt OR 'time limited') AND (psychotherapy* OR intervention* OR therapy OR therapies OR counsel* OR treatment* OR advice OR advisory OR motivate OR motivational) OR "alcohol sbi"
12	Treatment settings	exp Substance Abuse Treatment Centers/OR health facilities/ or exp community health centers/ or exp community mental health centers/ or exp outpatient clinics, hospital/ or exp secondary care centers/ or exp tertiary care centers/ or exp residential facilities/ OR exp primary health care/ or exp "Referral and Consultation"/ OR exp "delivery of healthcare"/ OR exp Community Mental Health Services/ or exp Mental Health Services/ or exp Health Care Services/ or exp Treatment Facilities/ or exp Psychiatric Hospitals/ or exp Community Mental Health Centers/OR exp clinics/ or exp psychiatric clinics/ or exp walk in clinics/ OR exp Therapeutic Environment/OR health care services/ or exp "continuum of care"/ or exp long term care/ or exp mental health services/ or exp primary health care/ or exp mental health programs/ or exp rehabilitation/ OR exp general practitioners/ OR ("primary care" or "primary health" or (family ADJ1 physician*) or (general ADJ1 practi*) or (family ADJ1 practi*) or outpatient* or clinic* or ambulatory or (health ADJ1 center*) or (health ADJ1 centre*) or office OR specialist* OR specialty OR rehab* OR inpatient OR "secondary care" OR "tertiary care" OR refer OR referral OR referred OR ((setting* OR facility OR facilities OR center OF centers) ADJ3 (treatment OR care OR therapy OR therapies))).ti,ab.
13	Patient selection criteria	Exp patient selection/ OR exp disease management/ OR exp Guideline Adherence/ or exp Guideline/ or exp Practice Guideline/ OR exp Treatment Guidelines/OR exp Evaluation Criteria/ OR exp client characteristics/ OR ((patient ADJ4 (criteria OR characteristic* OR selection)) OR (settin* ADJ3 (treatment OR care OR therapy OR therapies))).ti,ab.
14	Care Intensity	(('short term' OR 'long term' OR intense OR intensive OR intensity OR aggressive) ADJ3 (care OR treatment OR therapy OR therapies) OR 'level of care' OR 'levels of care').ti,ab.
15	Measurement based care	Exp *Self Report/ OR exp *Questionnaires/ OR exp *Biological Markers/ OR exp*Monitoring, Physiologic/ OR exp *Psychiatric Status Rating Scales OR exp *psychological tests/ or exp *psychometrics/ OR exp *health status indicators/ or exp *"severity of illness index"/ OR exp *measurement/ or exp *test scores/ or exp *testing methods/ OR exp*monitoring/ "Measurement based care" OR "addiction severity index" OR "brief addiction monitor" OR (measurement ADJ2 care) OR questionnaire*:ti OR scale:ti OR scales:ti OR instrument*:ti OR index:ti OR measure*:ti OR monitor*:ti OR assessment:ti OR assess:ti OR biomarker*ti OR "PHQ":ti,ab OR "patient health questionnaire" OR (continuous ADJ2 (monitor* OR assessment*)) OR (biological ADJ2 measure*)
16	Combine sets KQ 1	1 AND (6 OR 7)

Set Number	Concept	Search Statement
17	Combine sets KQ 2 (overlaps with KQ 3)	2 AND (6 OR 8)
18	Combine sets KQ 3 (overlaps with KQ 2)	2 AND 10
19	Combine sets KQ 4	1 AND 11
20	Combine sets KQ 5	1 AND 12 AND (13 OR 14)
21	Combine sets KQ 6 and 7, and psychosocial components of KQs 9 and 10	(1 OR 2 OR 3 OR 4 OR 5) AND 10
22	Combine sets KQ 8	(1 OR 2 OR 3 OR 4 OR 5) AND 15
23	Combine sets KQs 9, 10, and 11;	3 AND (6 OR 9)
24	For all searches - remove unwanted publication types/Apply limits	NOT (("column/opinion" OR "comment/reply" OR dissertation OR editorial OR letter OR book).dt. OR book.pt.) OR (letter/ or editorial/ or news/ or comment/ or case report or case reports/ or note/ or conference paper/) or (letter or editorial or news or comment or case reports or conference abstract$).pt. Py:2007-2014; humans; English language
25	For all searches - Limit to RCTs or SRs/Meta-Analyses	AND (Randomized controlled trials or random allocation or double-blind method or single-blind method or placebos or cross-over studies).de. or placebo$.mp. or random$.ti. or crossover$.mp. or cross over.mp. or ((singl* or doubl* or tripl* or trebl*) and (blind* or mask* or sham*)).mp. or latin square.mp. or ISRTCN or ACTRN* or (NCT* not NCT) or (clinical trials/ and random*.ti.) OR (meta analysis/ or (systematic review or meta analysis).md. or (meta-analysis or systematic review).ti.

OVID syntax:

$ or * = truncation character (wildcard)

ADJ*n* = search terms within a specified number (*n*) of words from each other in any order

/ = search as a subject heading (note that terms preceded by an asterisk are searched as a major subject headings)

exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.md. = type of methodology (PsycINFO)

.mp. = combined search fields (default if no fields are specified)

.pt. = publication type

.ti. = limit to title

.tw. = limit to title and abstract fields

Table H-3. Embase

Set Number	Concept	Search Statement
1	AUD	'Alcohol abuse'/exp OR 'alcohol use disorder'/exp OR alcoholism/exp OR 'drinking behavior'/exp OR 'alcohol abstinence'/exp OR 'alcohol withdrawal'/exp OR alcoholism:ti,ab OR (alcohol near/3 (abuse OR misuse OR intoxicat* OR addict*)):ti,ab OR alcoholics:ti,ab OR drunk:ti,ab OR drunken:ti,ab
2	OUD	'opiate addiction'/exp OR 'analgesic agent abuse'/exp OR (('drug abuse'/exp OR 'drug dependence'/exp OR 'narcotic dependence'/exp OR 'addiction'/exp) AND ('narcotic analgesic agent'/exp OR opiate* OR opioid* OR narcotic* OR hydrocodone OR vicodin OR oxycodone OR oxycontin OR percocet OR heroin OR methadone OR morphine OR codeine OR analgesic*))
3	Cannabis, cocaine, and stimulant use disorder	'cannabis addiction'/exp OR 'cocaine dependence'/exp OR (('drug abuse'/exp OR 'drug dependence'/exp OR 'addiction'/exp) AND ('cannabis'/exp OR 'cannabis use'/exp OR 'central stimulant agent'/exp OR 'amphetamine'/exp OR 'methamphetamine'/exp OR 'dexamphetamine'/exp OR 'cocaine'/exp)) OR ((amphetamine* OR cocaine OR methamphetamine OR dextroamphetamine OR dexamphetamine OR Dexedrine OR Adderall OR marijuana OR cannabis OR stimulant* OR "meth") NEAR/3 (abuse OR misuse OR addict* OR disorder* OR user OR users)):ti,ab
4	Sedative hypnotic use disorder	('hypnotic sedative agent'/exp OR 'sedative agent'/exp OR 'barbituric acid derivative'/exp OR 'benzodiazepine derivative'/exp) AND ('substance abuse'/exp OR 'drug dependence'/exp OR 'withdrawal syndrome'/exp OR addiction/mj) OR ((Hypnotic* OR sedative* OR Benzodiazepine* OR barbiturate* OR Barbiturates OR Butalbital OR Firoina OR Amytal OR Nembutal OR Seconal OR uppers OR Phenobarbital OR barbs OR Ativan OR Halcion OR Librium OR Valium OR Xanax OR downers OR Ambien OR zolpidem OR Sonata OR zaleplon OR Lunesta OR eszopiclone OR roofies OR roofinol) NEAR/3 (abuse OR misuse OR addict* OR disorder* OR user OR users)):ti,ab
5	General substance abuse terms	'substance abuse'/exp OR 'inhalant abuse'/exp OR 'intravenous drug abuse'/exp OR 'multiple drug abuse'/exp OR 'drug dependence'/exp OR 'withdrawal syndrome'/exp OR addiction/mj OR ((substance OR substances OR drug OR drugs OR polydrug*) NEAR/3 (abuse OR misuse OR addict* OR disorder* OR users)):ti,ab
6	Pharmacotherapy (broad terms)	'drug therapy'/exp OR drug therapy/lnk OR 'drug combination'/exp OR 'drug combination'/lnk OR 'drugs used in the treatment of addiction'/exp OR 'drug administration'/exp OR 'drug administration'/lnk OR 'drug comparison'/exp OR 'drug comparison'/lnk

Set Number	Concept	Search Statement
7	Pharmacotherapy (drug terms-alcohol use)	acamprosate OR disulfiram OR naltrexone OR atomoxetine OR baclofen OR buspirone OR citalopram OR desipramine OR fluoxetine OR fluvoxamine OR gabapentin OR imipramine OR nalmefene OR olanzapine OR ondansetron OR paroxetine OR quetiapine OR sertraline OR topiramate OR valproic acid OR varenicline
8	Pharmacotherapy (drug terms-opioid use)	'opiate agonist'/exp OR 'opiate receptor affecting agent'/exp OR 'alpha adrenergic receptor stimulating agent'/exp OR 'opiate antagonist'/exp OR buprenorphine OR naloxone OR methadone OR naltrexone OR "LAAM" OR 'levomethadyl acetate' OR clonidine OR lofexidine OR guanfacine OR guanabenz OR (alpha near/3 adrenergic)
9	Pharmacotherapy (drug terms-cannabis/stimulant/cocaine use)	'disulfiram'/exp OR 'topiramate'/exp OR disulfiram OR esperal OR dicupral OR disulfide OR alcophobin OR anticol OR Antabuse OR antabus OR teturam OR topiramate OR topamax OR topimax OR Bupropion OR Divalproex OR Nefazodone OR Tetrahydrocannabinol OR Lofexidine OR Dronabinol OR Modafinil OR 'opiate agonist'/exp OR 'opiate antagonist'/exp OR agonist/exp OR Baclofen OR agonist
10	Psychosocial Therapies	Psychotherapy/exp OR 'cognitive therapy'/exp OR counseling/exp OR 'Acceptance and commitment therapy'/exp OR 'support group'/exp OR 'motivational interviewing'/exp OR 'alcohol rehabilitation program'/exp OR 'alcoholics anonymous'/exp OR 'community based rehabilitation'/exp OR counsel OR counseling OR psychotherap*:ti,ab OR counseling:ti,ab OR ((cognitive OR behavioral OR motivational OR couples OR family OR group OR psychosocial) near/2 (counseling OR therapy)):ti,ab OR 'community reinforcement' OR 'contingency management' OR (motivation* near/2 interview*) OR (twelve NEXT/1 step) OR "alcoholics anonymous" OR "narcotics anonymous" OR "self help" OR ((mutual OR community) NEAR/1 (help OR group* OR support)):ti,ab OR (support NEAR/1 group*):ti,ab OR "12-step"
11	Brief interventions for alcohol use	'Short course therapy'/exp OR 'motivational interviewing'/exp OR (brief OR short OR concise OR abrupt OR 'time limited') near/4 (intervention* OR therapy OR therapies OR counsel* OR treatment* OR advice OR advisory OR motivate OR motivational) OR "alcohol sbi"
12	Treatment settings	'alcohol rehabilitation program'/exp 'rehabilitation'/de OR 'secondary health care'/exp OR 'health care facility'/de OR 'community mental health center'/exp OR 'health center'/exp OR 'mental health center'/exp OR 'rehabilitation center'/exp OR 'residential home'/exp OR 'secondary care center'/exp OR 'tertiary care center'/exp OR 'patient referral'/exp OR 'primary health care'/exp OR 'general practitioner'/exp OR 'primary care' or 'primary health' or (family NEXT/1 physician*) or (general NEXT/1 practi*) or (family NEXT/1 practi*) or outpatient* or clinic* or ambulatory or (health NEXT/1 center*) or (health NEXT/1 centre*) or office OR specialist* OR specialty OR rehab* OR inpatient OR 'secondary care' OR 'tertiary care' OR refer OR referral OR referred OR ((setting* OR facility OR facilities OR center OR centers) NEAR/3 (treatment OR care OR therapy OR therapies)):ti,ab
13	Patient selection criteria	'patient selection'/exp OR 'disease management'/exp OR 'practice guideline'/exp OR 'patient care planning'/exp OR ((patient NEAR/4 (criteria OR characteristic* OR selection)):ti,ab OR (settin* NEAR/3 (treatment OR care OR therapy OR therapies):ti,ab

Set Number	Concept	Search Statement
14	Care Intensity	(('short term' OR 'long term' OR intense OR intensive OR intensity OR aggressive) NEAR/3 (care OR treatment OR therapy OR therapies)) OR 'level of care' OR 'levels of care'
15	Measurement based care	"Measurement based care" OR 'self report'/exp/mj OR 'psychological rating scale'/exp/mj OR 'questionnaire'/exp/mj OR 'biological marker'/exp/mj OR parameters/de OR 'patient monitoring'/de OR 'named inventories, questionnaires and rating scales'/exp/mj OR 'self monitoring'/exp/mj OR 'Patient Health Questionnaire'/exp/mj OR "addiction severity index" OR "brief addiction monitor" OR (measurement NEXT/2 care) OR questionnaire*:ti OR scale:ti OR scales:ti OR instrument*:ti OR index:ti OR measure*:ti OR monitor*:ti OR assessment:ti OR assess:ti OR biomarker*ti OR "PHQ":ti,ab OR "patient health questionnaire" OR (continuous NEAR/2 (monitor* OR assessment*)) OR (biological NEAR/2 measure*)
16	Combine sets KQ 1	1 AND (6 OR 7)
17	Combine sets KQ 2 (overlaps with KQ 3)	2 AND (6 OR 8)
18	Combine sets KQ 3 (overlaps with KQ 2)	2 AND 10
19	Combine sets KQ 4	1 AND 11
20	Combine sets KQ 5	1 AND 12 AND (13 OR 14)
21	Combine sets KQ 6 and 7, and psychosocial components of KQs 9 and 10	(1 OR 2 OR 3 OR 4 OR 5) AND 10
22	Combine sets KQ 8	(1 OR 2 OR 3 OR 4 OR 5) AND 15
23	Combine sets KQs 9, 10, and 11;	3 AND (6 OR 9)
24	For all searches - remove unwanted publication types/Apply limits	NOT ('conference paper'/exp OR 'case study'/exp ('case report' OR book OR editorial OR erratum OR letter OR note OR 'short survey')/de OR (book OR conference OR editorial OR erratum OR letter OR note OR 'short survey'):it OR (book OR 'conference proceeding'):pt) Limits: Py:2007-2015; humans; English language
25	For all searches - Limit to RCTs or Systmatic Reviews/Meta-Analyses	AND ('randomized controlled trial'/exp OR 'randomization'/de OR 'double blind procedure'/de OR 'single blind procedure'/de OR 'placebo'/de OR 'crossover procedure'/de OR placebo* OR random*:de,ti OR crossover* OR 'cross over' OR (singl* OR doubl* OR tripl* OR trebl* AND (blind* OR mask* OR sham*)) OR 'latin square' OR isrtcn* OR actrn* OR (nct* NOT nct)) OR 'meta analysis'/de OR 'systematic review'/de OR 'meta analysis':ab,ti OR 'systematic review':ab,ti

EMBASE.com Syntax:

* = truncation character (wildcard)

NEAR/*n* = search terms within a specified number (*n*) of words from each other in any order

NEXT/*n* = search terms within a specified number (*n*) of words from each other in the order specified

/ = search as a subject heading

exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

mj = denotes a term that has been searched as a major subject heading

:de = search in the descriptors field (controlled terms and keywords)

:lnk = floating subheading

:it,pt. = source item or publication type

:ti. = limit to title

:ti,ab. = limit to title and abstract fields

Table H-4. PUBMED (PreMEDLINE)

Set Number	Concept	Search Statement
1	AUD	"Alcohol-Related Disorders"[Mesh] OR alcoholism[tiab] OR alcoholics[tiab] OR drunk[tiab] OR drunken[tiab] OR (alcohol[tiab] AND (abuse[tiab] OR misuse[tiab] OR intoxicat*[tiab] OR addict*[tiab] OR disorder*[tiab] OR dependence[tiab] OR dependent[tiab]))
2	OUD	"Opioid-Related Disorders"[Mesh] OR ((opioid*[tiab] OR narcotic*[tiab] OR hydrocodone[tiab] OR vicodin[tiab] OR oxycodone[tiab] OR oxycontin[tiab] OR Percocet[tiab] OR heroin[tiab] OR methadone[tiab] OR morphine[tiab] OR codeine[tiab] OR analgesic[tiab]) AND (abuse[tiab] OR misuse[tiab] OR intoxicat*[tiab] OR addict*[tiab] OR disorder*[tiab] OR dependence[tiab] OR dependent[tiab]))
3	Cannabis, cocaine, and stimulant use disorder	"Amphetamine-Related Disorders"[Mesh] OR "Cocaine-Related Disorders"[Mesh] OR "Marijuana Abuse"[Mesh] OR ("Central Nervous System Stimulants"[majr] AND "Substance-Related Disorders"[majr]) OR ((amphetamine*[ti] OR cocaine[ti] OR methamphetamine[ti] OR dextroamphetamine[ti] OR Dexedrine[ti] OR Adderall[ti] OR marijuana[ti] OR cannabis[ti] OR stimulant*[ti] OR "meth"[ti]) AND (abuse[ti]OR misuse[ti] OR addict*[ti] OR disorder*[ti] OR user[ti] OR users[ti]))
4	Sedative hypnotic use disorder	("Hypnotics and Sedatives"[Mesh] OR "Barbiturates"[Mesh] OR "Benzodiazepines"[Mesh]) AND ("Substance Abuse, Intravenous"[Mesh] OR "Substance Withdrawal Syndrome"[Mesh] OR "Substance-Related Disorders"[Mesh]) OR ((Hypnotic* OR sedative* OR Benzodiazepine* OR barbiturate*[tiab] OR Barbiturates[tiab] OR Butalbital[tiab] OR Firoina OR Amytal OR Nembutal OR Seconal OR uppers OR Phenobarbital OR barbs OR Ativan OR Halcion OR Librium OR Valium OR Xanax OR downers OR Ambien OR zolpidem OR Sonata OR zaleplon OR Lunesta OR eszopiclone OR roofies OR roofinol) AND (abuse[tiab] OR misuse[tiab] OR addict*[tiab] OR disorder*[ti] OR users[ti]))

Set Number	Concept	Search Statement
5	General substance abuse terms	"Inhalant Abuse"[Mesh] OR "Substance Abuse, Intravenous"[Mesh] OR "Substance Withdrawal Syndrome"[Mesh] OR "Substance-Related Disorders"[Mesh] OR ((alcohol[ti] OR substance[ti] OR substances[ti] OR drug[ti] OR drugs[ti]) AND (abuse[tiab] OR misuse[tiab] OR addict*[tiab] OR disorder*[ti] OR users[ti]))
6	Pharmacotherapy (broad terms)	"Drug Therapy"[Mesh] OR "drug therapy" [Subheading] OR pharmacotherap* OR ((drug[ti] OR drugs[ti] OR medication*[ti] OR prescription*[ti]) AND (treatment*[ti] OR treat[ti] OR treats[ti] OR therapy[ti] OR therapeutic*[ti]))
7	Pharmacotherapy (drug terms-alcohol use)	acamprosate[tiab] OR disulfiram[tiab] OR naltrexone[tiab] OR atomoxetine[tiab] OR baclofen[tiab] OR buspirone[tiab] OR citalopram[tiab] OR desipramine[tiab] OR fluoxetine[tiab] OR fluvoxamine[tiab] OR gabapentin[tiab] OR imipramine[tiab] OR nalmefene[tiab] OR olanzapine[tiab] OR ondansetron[tiab] OR paroxetine[tiab] OR quetiapine[tiab] OR sertraline[tiab] OR topiramate[tiab] OR 'valproic acid'[tiab] OR varenicline[tiab]
8	Pharmacotherapy (drug terms-opioid use)	"Adrenergic alpha-Agonists"[Mesh] OR "Adrenergic alpha-Agonists" [Pharmacological Action] OR buprenorphine[tiab] OR naloxone[tiab] OR methadone[tiab] OR naltrexone[tiab] OR "LAAM"[tiab] OR 'levomethadyl acetate'[tiab] OR clonidine[tiab] OR lofexidine[tiab] OR guanfacine[tiab] OR guanabenz[tiab] OR (alpha[tiab] AND adrenergic*[tiab])
9	Pharmacotherapy (drug terms-cannabis/stimulant/cocaine use)	Bupropion OR divalproex OR nefazodone OR tetrahydrocannabinol OR lofexidine OR dronabinol OR modafinil OR disulfiram OR esperal OR dicupral OR disulfide OR alcophobin OR anticol OR Antabuse OR antabus OR teturam OR Topiramate OR topamax OR topimax OR agonist OR agonists
10	Psychosocial Therapies	"Psychotherapy"[Mesh] OR "Self-Help Groups"[Mesh] OR "Couples Therapy"[Mesh] OR "Motivational Interviewing"[Mesh] OR "Counseling"[Mesh] OR psychotherap*[tiab] OR psychosocial[tiab] OR counseling[tiab] OR ((cognitive[tiab] OR behavioral[tiab] OR motivational[tiab] OR couples[tiab] OR family[tiab] OR group) AND (counseling[tiab] OR therapy[tiab])) OR "community reinforcement"[tiab] OR "contingency management"[tiab] OR "motivational interview"[tiab] OR "motivational interviewing"[tiab] OR "twelve step"[tiab] OR "support group"[tiab] OR "alcoholics anonymous" OR "narcotics anonymous" OR "self help" OR ((mutual[ti] OR community[ti]) AND (help[ti] OR group*[ti] OR support[ti]))
11	Brief interventions for alcohol use	(brief[tiab] OR short[tiab] OR concise[tiab] OR abrupt[tiab] OR 'time limited'[tiab]) AND (intervention*[tiab] OR therapy[tiab] OR therapies[tiab] OR counsel*[tiab] OR treatment*[tiab] OR advice[tiab] OR advisory[tiab] OR motivate[tiab] OR motivational[tiab]) OR "alcohol sbi"
12	Treatment settings	"Substance Abuse Treatment Centers"[Mesh] OR "health facilities"[Mesh] or "community health centers"[Mesh] OR "community mental health centers"[Mesh] OR "Outpatient Clinics, Hospital"[Mesh] or "secondary care centers"[Mesh] or "tertiary care centers"[Mesh] OR "residential facilities"[Mesh] OR "primary health care"[Mesh] OR "Referral and Consultation"[Mesh] OR "delivery of healthcare"[Mesh] OR ((Primary[tiab] OR secondary[tiab] OR tertiary[tiab] OR general[tiab]) AND (care[tiab] OR physician*[tiab] OR practice*[tiab] OR practitioner*[tiab])) or outpatient*[tiab] or clinic*[tiab] or

Set Number	Concept	Search Statement
		ambulatory[tiab] or "health center"[tiab] or office[tiab] OR specialist*[tiab] OR specialty[tiab] OR rehab*[tiab] OR inpatient*[tiab] OR refer[tiab] OR referral[tiab] OR referred[tiab] OR ((setting*[tiab] OR facility[tiab] OR facilities[tiab] OR center[tiab] OR centers[tiab]) AND (treatment[tiab] OR care[tiab] OR therapy[tiab] OR therapies[tiab]))
13	Patient selection criteria	(("Patient Selection"[Mesh]) AND "Disease Management"[Mesh]) OR ("Guidelines as Topic"[Mesh] OR "Practice Guidelines as Topic"[Mesh] OR "Guideline Adherence"[Mesh]) (patient[tiab] AND (criteria[tiab] OR characteristic*[tiab] OR selection[tiab])) OR (settin*[tiab] AND (treatment[tiab] OR care[tiab] OR therapy[tiab] OR therapies[tiab]))
14	Care Intensity	(("short term"[tiab] OR "long term"[tiab] OR intense[tiab] OR intensive[tiab] OR intensity[tiab] OR aggressive[tiab]) AND (care[tiab] OR treatment[tiab] OR therapy[tiab] OR therapies[tiab])) OR "level of care"[tiab] OR "levels of care"[tiab]
15	Measurement based care	"Self Report"[majr] OR Questionnaires[majr] OR "Biological Markers"[majr] OR "Monitoring, Physiologic"[majr] OR "Psychiatric Status Rating Scales"[majr] OR "psychological tests"[majr] OR psychometrics[majr] OR "health status indicators"[majr] OR "severity of illness index"[majr] OR "Measurement based care" OR "addiction severity index" OR "brief addiction monitor" OR (measurement*[tiab] AND care[tiab]) OR questionnaire*[ti] OR scale[ti] OR scales[ti] OR instrument*[ti] OR index[ti] OR measure*[ti] OR monitor*[ti] OR assessment[ti] OR assess[ti] OR biomarker*[ti] OR "PHQ"[tiab] OR "patient health questionnaire" OR (continuous[tiab] AND (monitor*[tiab] OR assessment*[tiab])) OR (biological[tiab] AND measure*[tiab])
16	Combine sets KQ 1	1 AND (6 OR 7)
17	Combine sets KQ 2 (overlaps with KQ 3)	2 AND (6 OR 8)
18	Combine sets KQ 3 (overlaps with KQ 2)	2 AND 10
19	Combine sets KQ 4	1 AND 11
20	Combine sets KQ 5	1 AND 12 AND (13 OR 14)
21	Combine sets KQ 6 and 7, and psychosocial components of KQs 9 and 10	(1 OR 2 OR 3 OR 4 OR 5) AND 10
22	Combine sets KQ 8	(1 OR 2 OR 3 OR 4 OR 5) AND 15
23	Combine sets KQs 9, 10, and 11;	3 AND (6 OR 9)
24	For all searches - remove unwanted publication types/Apply limits	NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR "Textbooks" [pt] OR "Book Reviews"[pt]OR "Book Illustrations"[pt]) Limits: Py:2007-2015; humans; English language
25	For all searches - Limit to RCTs or Systematic Reviews/Meta-Analyses	AND ((Random*[tiab] OR randomized[tiab] OR RCT*[tiab]) OR (meta-analysis[tiab] OR meta-analysis[pt] OR systematic*[tiab] OR "systematic review"[tiab]))

Set Number	Concept	Search Statement
26	Limit to "In process" citations [i.e. citations that have not yet been indexed and therefore may not have been captured in the MEDLINE search]	AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])

PubMed syntax:

[Mesh] = search as a subject heading

[majr] = search as a major subject heading

* = truncation character (wildcard)

[ti] = limit to title field

[tiab] = limit to title and abstract fields

[tw] = text word

Appendix I. Acronym List

Abbreviation	Definition
AA	Alcoholics Anonymous
AHRQ	Agency for Healthcare Research and Quality
ASAM	American Society of Addiction Medicine
AUD	alcohol use disorder
AUDIT-C	Alcohol Use Disorders Identification Test - Consumption
AUDIT-PC	Alcohol Use Disorders Identification Test Primary Care
AWS	alcohol withdrawal syndrome
BAL	blood alcohol level
BCT	Behavioral Couples Therapy
BI	brief intervention
BT	behavioral therapy
CBT	Cognitive Behavioral Therapy
CDC	Centers for Disease Control and Prevention
CENTRAL	The Cochrane Central Register of Controlled Trials
CIWA-Ar	Clinical Institute Withdrawal Assessment for Alcohol (revised version)
CKD	chronic kidney disease
CM	Contingency Management
Cmax	maximum concentration
CMI	chronic multisymptom illness
CNS	central nervous system
COR	contracting officer's representative
COWS	Clinical Opiate Withdrawal Scale
CPG	clinical practice guideline
CRA	Community Reinforcement Approach
CrCl	creatinine clearance
DATA 2000	Drug Addiction Treatment Act of 2000
DEA	Drug Enforcement Administration
DoD	Department of Defense
DODD	Department of Defense Directive
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EBPWG	Evidence-Based Practice Work Group
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HTA	Health Technology Assessment Database

Abbreviation	Definition
KQ	key question
LARS	Luebeck Alcohol Withdrawal Risk Scale-11
m	meter(s)
MDD	major depressive disorder
MeSH	Medical Subject Headings
MET	Motivational Enhancement Therapy
mg	milligram(s)
MI	motivational interviewing
mL	milliliter(s)
MMT	methadone maintenance therapy
mTBI	mild traumatic brain injury
NA	Narcotics Anonymous
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NICE	National Institute for Health and Care Excellence
NIDA	National Institute on Drug Abuse
NS	Network Support
OAT	opioid agonist therapy
OBOT	Office-based Opioid Therapy
OTP	Opioid Treatment Program
OUD	opioid use disorder
PACT	Patient-aligned Care Team
PAWSS	Prediction of Alcohol Withdrawal Severity Scale
PC-MHI	Primary Care-Mental Health Integration
PCT	person-centered therapy
PDMP	prescription drug monitoring program
PHQ-9	Patient Health Questionnaire
PICOTS	population, intervention, comparison, outcome, timing and setting
PRN	as needed
PTSD	posttraumatic stress disorder
QTc	the heart rate corrected time from the start of the Q wave to the end of the T wave
RCT	randomized controlled trial
SAMHSA	Substance Abuse and Mental Health Services Administration
SASQ	Single Item Alcohol Screening Questionnaire
SAWS	Short Alcohol Withdrawal Scale
SDM	shared decision making
SR	systematic review
SUD	substance use disorders
TAU	treatment as usual
TJC	The Joint Commission
TSF	12-Step Facilitation

Abbreviation	Definition
U.S.	United States
USPSTF	U.S. Preventive Services Task Force
VA	Department of Veterans Affairs

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