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 Department of Veterans Affairs or 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 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 Committee (HEC) "…on the use of clinical and epidemiological evidence to improve the health of the population…" across the Veterans Health Administration (VHA) and Military Health System (MHS), by facilitating the development of clinical practice guidelines (CPGs) for the VA and DoD populations.(1) Development and update of VA/DoD CPGs is funded by VA Evidence Based Practice, Office of Quality and Patient Safety. The system-wide goal of evidence-based CPGs is to improve patient health and well-being.

In 2015, the VA and DoD published a CPG for the Management of Substance Use Disorders (2015 VA/DoD SUD CPG), which was based on evidence reviewed from November 2007 through January 2015. The 2015 VA/DoD SUD CPG updated the 2009 VA/DoD CPG and for the first time addressed substance use disorder care in non-addiction care settings. Since the release of that CPG, a growing body of research has continued to inform evidence-based practices for the screening, assessment, and treatment of substance use disorders (SUD).[a] Consequently, a recommendation to update the 2015 VA/DoD SUD CPG was initiated in 2020.

This CPG provides an evidence-based framework for evaluating, treating, and managing the individual needs of patients with SUD in the VA and DoD. It is intended for use by all VA and DoD healthcare providers. Successful implementation of this CPG will:

- Assist providers in assessing the patient's condition and collaborating with the patient, their family, and their caregivers to determine optimal management of patient care
- Emphasize the use of patient-centered care
- Minimize preventable complications and morbidity
- Optimize individual health outcomes and quality of life

II. Background

A. Description of Substance Use Disorders

Substance use disorders can develop in individuals who use alcohol or other addictive drugs. About 3% of Americans over age 12 have an illicit drug use disorder (including cannabis) and about 5.3% have an alcohol use disorder (AUD); however only about 12.2% of individuals who need treatment receive SUD specialty care.(2) One in every four Americans will develop a non-nicotine- or tobacco-related SUD during their lifetime.(3, 4) Alcohol consumption is one of the leading preventable causes of death in the United States (U.S.), with over 95,000 annual deaths attributable to alcohol involving acute (e.g., motor vehicle accidents) and chronic conditions (e.g., liver disease, cancer, heart disease).(5)

Substance use disorders (including tobacco) are among the leading causes of death in the U.S.(6) Substance use costs the U.S. $600 billion annually, but participation in treatment helps to offset these costs.(7) While the costs to our nation from SUD are high, healthcare professionals are in a unique position

[a] In this CPG, the term SUD encompasses AUD, OUD, sedative hypnotic use disorder, stimulant use disorder, and cannabis use disorder.

to improve the health and wellbeing of the Service Members and Veterans they treat by implementing effective SUD prevention and treatment strategies.

The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) describes an SUD as a problematic pattern of use leading to clinically significant impairment or distress.(8) This loss of control over substance use can lead to a change in how the brain functions and can cause other long-term health problems (e.g., cardiovascular disease, stroke, and lung disease).(9) It can also limit the ability of individuals to fulfill their professional or personal life roles and can have other legal, social, or physical ramifications.(10, 11) The DSM-5 defines SUD using 11 diagnostic criteria.(8) The severity of SUD is characterized 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, and memory) involved in obtaining natural rewards such as food, water, or social support that are essential for survival. Addictive substances mimic the brain's natural neurotransmitters and neuromodulators, interfere with the brain's regulation of its normal functions, or both, generating a false reward learning signal.(13) This activity changes the reward system in patients with SUD. When functioning normally, the mesolimbic dopamine pathway, which is a key component of the brain's reward system, trains a person to seek contexts in which they have previously experienced rapid improvements in well-being. Connections between mesolimbic dopamine and memory circuits enable a person to remember the people, places, and things associated with the reward.

Addictive substances artificially activate mesolimbic dopamine pathways such that reward circuits are taught that drug use is always more rewarding than expected. With sufficient repeated use of addictive substances, they become over-valued compared to natural rewards and one can develop an SUD. 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 impulse to use substances increases even as negative consequences of use increase.(14) Negative affect states associated with withdrawal and chronic use become increasingly common and may drive additional drug seeking for relief.(15) This cascade 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 2019, approximately 20.4 million Americans met the criteria for SUD. Of those, 14.5 million had AUD, and 8.3 million had an illicit drug use disorder.(2)

Tobacco is the substance responsible for the most deaths in the U.S. The U.S. Centers for Disease Control and Prevention (CDC) reports that more than 480,000 Americans die from the effects of tobacco use each year.(16) Further, smoking reduces life expectancy by at least 10 years. The Work Group acknowledges that tobacco use disorder is a significant problem; however, it is not the focus of this CPG. See the corresponding section on Substance Use Disorder and Tobacco Use below for more information.

The CDC also reports that at least 95,000 Americans die prematurely each year from alcohol use due to disease, accidents, and suicide.(5) An additional 70,630 people died of drug overdoses in 2019, greatly exceeding the number who died of suicide.(17) At the time of publication, 2020 data was not available; however, the CDC estimates that 2020 deaths due to overdose will exceed all previous years.

In 2019, 49,860 Americans died of opioid overdose,(17) exceeding the 46,802 Americans who died of opioid overdose in 2018 and over twice as many as the 21,088 Americans who died of opioid overdose in 2010.(18) The 2018 number is only slightly less than the 48,344 individuals who died by suicide in 2018, making opioid overdose alone the 11th most common cause of death in the U.S. Non-methadone synthetic opioids such as fentanyl were the primary cause of death by opioid overdose.(5) Roughly twice as many men than women die of opioid overdose.(18)

Death by psychostimulant overdose is the next most common cause of overdose death. For the first time, deaths from methamphetamine overdose exceeded deaths from cocaine overdose, with approximately 16,100 Americans dying of methamphetamine overdose and an additional 15,900 Americans dying of cocaine overdose in 2019.(17, 19)

C. Factors Affecting Risk of Substance Use Disorders

The risk of a person developing SUD is affected by several factors. One factor is biology, including genetic make-up, gender, and the presence of other comorbidities. For instance, rates of alcohol and drug use disorders in males are nearly double that in females.(20) In 2012 – 2013, 12-month and lifetime prevalence of AUD were higher for people who identified as white and Native American.(21) There is also an increased risk for developing other substance use and mental health disorders if a relative is affected by SUD.(20)

Other factors that may affect the development of SUD 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 SUD peaks in late adolescence and early adulthood, and starts to decrease after age 26.(20) In addition, those who initiated substance use earlier in their lives are more likely to be affected by SUD in adulthood.(22) Socioeconomic status, SUD in family and friends, and quality of life can also influence risk.(23)

There is, however, evidence suggesting the Baby Boomer generation will have the highest rates of SUD diagnosis, outstripping the rates of diagnosis in the teen/early adult population.(24, 25) This is likely due to a combination of factors including a cultural shift in the 1960s – 1970s with increased availability and acceptability of illicit substance use, increased rates of prescription opioid use in the 1990s and early 2000s, and increased acceptability of SUD treatment.

Substance use disorders represent a rising problem among older adults. The 2019 National Survey of Drug Use and Health (NSDUH) conveys the landscape of substance use among older adults.(2) Individuals aged 60 – 64 reported rates of past month illicit drug use of 11.1% with individuals aged 65 and older reporting past month rates of 4.2%.(2) Marijuana, which many states have legalized, accounts for most of this use with past month rates of 9.8% and 3.5% in these age groups respectively.(2) Legalization is associated with increased rates of marijuana use among adults age 26 and over,(26) with concern that it is also associated with increases being seen in older adults, though this topic needs direct study. Misuse of opioids in the past month is reported by 1.0% and 0.5 % of these age groups, respectively. Regarding alcohol, the most common substance used by older adults, 52.8% of adults ages 60 – 64 and 43.9% of 65 and older report use in the past month, with rates of binge drinking of 19.7% and 10.7% in the past month, respectively.

Aging heightens the risks of substance use including higher risk for toxicity because of a slowing metabolism, higher risk for physical injury because of aging-related decrements in motor coordination,

higher risk for confusion and cognitive impairment related to intoxication, and higher risk for adverse effects of drug use on existing chronic health conditions.

No studies examine specific treatments for SUD among older adults, so providers should consider the same evidence-based treatments that work for the general adult population.

However, as with all adults, older adults often do not receive appropriate treatment even when engaged in the treatment system. For example, recent work examined admissions to SUD treatment for heroin using adults over age 55.(27) It subtyped these older heroin users into those who had "typical" or early onset of use before age 30 and those who had late onset use after age 30. The study found the early onset group had higher rates of use of other substances and heroin injection. Rates of receiving medication treatment for opioid use disorder (OUD), which is the only evidence-based treatment, hovered just below 70% for the early onset group and just above 30% for the late onset. Other recent work shows that in a primary care setting among individuals with diagnosed OUD, older age was associated with less likelihood of getting medication treatment.(28) These inadequate rates of medication treatment present a missed opportunity that could be addressed with greater engagement of providers in prescribing FDA-approved medications for OUD.

High rates of alcohol and marijuana use among older adults, while perhaps not as serious as injection opioid use, also need to be addressed. Heavy alcohol consumption is even more pronounced among older adults in many European countries than in the U.S.(29) Alcohol-related mortality is increasing in the U.S., including in older people. Excessive alcohol use (not necessarily use that rises to the level of AUD) is associated with many health problems that plague older individuals, including cardiac disease, cancer, and dementia. It is incumbent upon providers treating older adults to inquire about alcohol use and counsel safe amounts of consumption. Many older adults do not know that greater levels of consumption are hazardous and they may voluntarily reduce their use when educated. Such reductions are likely to reduce morbidity and mortality in this population.

While the effects of marijuana/cannabis use in older adults specifically have not received adequate investigation, the known adverse effects (including cognitive and motor impairment, possible increased risk for cardiovascular events, alterations in sleep, appetite, and mood, as well as cannabis withdrawal symptoms) are likely to be even more problematic in this age group compared to younger adults.

Many older adults also use multiple substances, with alcohol, marijuana, sedatives, and stimulants likely among them.(27) Thus, providers who treat older adults face challenges in detection, assessment, and management of older adult patients who use multiple substances. Our entire healthcare system must gear up to surmount this ever-worsening opioid and substance use epidemic among older adults.

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

Substance use disorders account for substantial morbidity and excess mortality in the general population and are widely recognized as a healthcare concern for Veterans.(30, 31) The 2019 NSDUH found 1.3 million Veterans (6.2%) had an SUD and among those with an SUD, 26.9% struggled with illicit drugs, 80.8% with alcohol use, and 7.7% with both illicit drugs and alcohol.(32) Among illicit drug use, marijuana was the most used drug followed by psychotherapeutic drugs (pain relievers, tranquilizers, stimulants, and sedatives), cocaine, hallucinogens, methamphetamine, heroin, and inhalants.(32) Opioid misuse, defined

as use not directed by a physician, was noted among 595,000 Veterans (2.9% of the total Veteran population) with 555,000 related to prescription opioid misuse (e.g., hydrocodone, oxycodone, fentanyl), 57,000 related to heroin misuse, and 16,000 for both heroin and prescription opioid misuse.(32) Despite the significant prevalence of SUD among Veterans, only about 15% of Veterans with an SUD receive treatment such as a hospital (inpatient), rehabilitation facility (inpatient or outpatient), mental health center, emergency room, private doctor's office, self-help group, or prison/jail.(32)

Substance use disorders are common among VA patients, and they are costly. Among VA patients, non-tobacco and non-nicotine SUD is increasing in absolute terms and as a percentage of VA patients, from more than 270,000 patients (6.1% of VA patients) in 2002 (33) to 580,000 (8.3% of VA patients) in 2019.(34) Substance use disorders are more common among younger, male patients, mirroring population patterns for non-Veterans.(35, 36)

In addition, SUD commonly co-occurs with and complicates other conditions or issues such as homelessness, criminal justice involvement, or unemployment. Substance use disorders are also more common among patients with a history of trauma or co-occurring physical or mental health conditions,(37) and, conversely, patients with SUD are at increased risk for adverse physical health consequences, mental health symptoms, cognitive impairment, and early mortality.(35, 38-40)

The 2019 NSDUH estimates that 2.3% of Veterans have both an SUD and mental illness.(32) Additionally, 16.8% of Veterans with probable posttraumatic stress disorder (PTSD) had probable AUD,(41) and among Veterans of the Iraq and Afghanistan wars who used VHA health care, PTSD was present in 63% of those with AUD, in 63.4% with drug use disorder, and 76.1% with both AUD and drug use disorder.(37, 42) Furthermore, roughly 33% and 22% of Veterans experiencing homelessness have 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.(43)

Alcohol misuse is a major concern in the DoD. Not only are matriculated active duty Service Members drawn from the heaviest drinking U.S. demographic both by gender (predominantly male) and by age group (late adolescence and early adulthood), but binge drinking and heavy drinking occur at higher rates among those in uniform compared to their civilian counterparts.(44) Also, per above, this predominantly young, male demographic group is one in which the still-developing brain is particularly vulnerable to substance use and risks long-term damage from it.(44)

Up to 27% of Soldiers returning from war have problems related to alcohol use.(45) These combat-exposed Soldiers and Marines also have high rates of PTSD and depression,(46) problems that alcohol use may worsen. Alcohol problems also contribute heavily to problems of indiscipline (e.g., missed duty and driving while intoxicated), which erode readiness, end careers, and impact individuals and families.(45) The Army and Marine Corps are the Services whose members tend to have the most combat exposures; such combat exposures are correlated with higher rates of alcohol problems, PTSD, and depression. It is therefore fitting that both Services also use independently credentialed mental health providers (e.g., licensed clinical social workers, licensed professional counselors) to provide direct evaluation and treatment for Service Members with substance use problems.

The DoD has substantially lower rates of illicit substance use than civilian or VA populations.(31) This is largely attributed to effective deterrence: the Uniform Code of Military Justice (UCMJ), which outlaws it, a

sophisticated system of random urine drug screening that detects it, and Command authorities who either prosecute or separate the Service Member who has not self-identified their substance use and come forward for treatment.

Although alcohol is not an illegal substance, getting Service Members to come forward for treatment for alcohol misuse is complicated by DoD-wide guidance that substance use treatment must occur during a formal enrollment in mandatory care, and with the Service Member's commander, who is also their legal authority being involved in the treatment.(47) Such treatment is tracked in personnel databases and can impact assignments and career progression. This risk of adverse career impact creates understandable stigma, especially among career-oriented Service Members, towards substance use care.

This stigma likely handicaps the effectiveness of alcohol screening that occurs in military health clinics; the vast body of civilian research done on the three question Alcohol Use Disorders Identification Test - Consumption (AUDIT-C) screening for the identification of and early intervention for alcohol problems did not include screening in a military setting.(48) Of note, in a review of substance use in the DoD, the Institute of Medicine (IOM) (now the National Academy of Medicine [NAM]) recommended that a voluntary care track for alcohol care, having the same Health Insurance Portability and Accountability Act of 1996 (HIPAA) protections as other medical and behavioral health care, be established DoD-wide for Service Members who had not had an alcohol-related disciplinary problem (e.g., a DUI).(31) The Army established such a program in 2019, which has already produced positive results by increasing the readiness of Service Members for potential deployment and by decreasing the rate of emergency service alcohol-related visits.(49, 50)

E. Strategies to Promote Engagement in Treatment

A fundamental goal of this CPG is to promote early engagement and retention of patients with SUD who can benefit from addiction-focused treatment. Many patients may initially decline voluntary referral (51) or may not be interested or engaged in treatment, 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 (e.g., 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.(52) Therefore, attention to these general therapeutic factors is at least as important as the specific treatment approach selected.(53)

Apart from the evidence-based recommendations of this guideline, the following strategies are felt to be fundamental to the engagement/re-engagement process for patients with SUD:

- Indicate to the patient and significant others that treatment is more effective than no treatment (i.e., "treatment works")
- Consider the patient's prior treatment experience and respect patient preference for psychosocial/psychopharmacologic intervention approach(es)
- Use a motivational interviewing (MI) style during therapeutic encounters with patients (54-56) 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, supporting a healthy lifestyle, and enhancing social support for recovery

- Emphasize that the most consistent predictors of successful outcomes are retention in treatment and/or active involvement with community support for recovery
- Use strategies demonstrated to be efficacious to promote active involvement in available mutual help programs (e.g., Alcoholics Anonymous [AA], Narcotics Anonymous [NA])
- Coordinate evidence-based, addiction-focused psychosocial/psychopharmacologic intervention(s) to address identified concurrent biopsychosocial problems, consistent with patient priorities
- Provide intervention in the setting most likely to promote access to safe and effective care
- Do not automatically discharge patients from care who do not respond to treatment or who return to use
- If a patient drops out of treatment, the health care team should make efforts to contact the patient and re-engage him/her in treatment
- 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. Substance use disorder is a chronic illness. As such, the management approach should be consistent with many other disorders treated in medical and psychiatric settings.(57-59)

F. Addiction-focused Medical Management in the Primary Care Setting

Effective evidence-based medication treatments are available for SUD, particularly AUD and OUD. Addiction-focused medical management is a manualized psychosocial intervention designed to be delivered by a medical professional (e.g., physician, nurse, physician assistant, clinical pharmacy specialist) in support of evidence-based medication treatment.(60) The treatment provides strategies to increase medication adherence and monitoring of substance use and consequences, as well as supporting abstinence through motivational strategies, education, and referral to support groups.

While variably defined, addiction-focused medical management typically includes:(61-64)

1. Review of self-reported use, laboratory markers, and consequences, and praise of small steps toward recovery goals
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 adherence. An initial session may involve a 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.

Initially, follow-up sessions can be 15 – 20 minutes weekly, or as clinically indicated. Depending on patient stability, follow-up sessions can be less frequent and possibly via telemedicine. When the patient does not adhere to the medication regimen, the clinician takes a non-judgmental, problem-solving approach to evaluate the reasons and helps the patient devise plans to address the problem(s). Clinicians can praise small steps toward recovery and offer common sense recommendations to mitigate return to use risk, such as avoiding specific situations like going to bars. If the patient experiences medication side effects, the clinician specifies procedures for using concomitant or alternate medication to ameliorate them or reduces the dosage of medication. If a patient discontinues medication because he or she cannot tolerate it, the clinician can schedule 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.

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

The DoD specifies, "substance abuse[b] by military personnel is inconsistent with the [DoD's] Values, the Warrior Ethos, and the standards of performance, discipline, and readiness necessary to accomplish the DoD's mission."(65) On September 28, 1971, Public Law (PL) 92-129, mandated that the U.S. Secretary of Defense develop programs for the identification, treatment, and rehabilitation of alcohol or other substance-dependent persons in the Armed Forces.(66) In turn, the Secretary of Defense requires each Service to develop alcohol and other substance abuse prevention and control programs per DoD Directive (DODD) 1010.4.(67) In response to these directives, the DoD conducts comprehensive programs to prevent and control the misuse of alcohol and other substances. The Service-specific programs are designed to strengthen the overall fitness and effectiveness of Service Members, conserve manpower, enhance combat readiness, and increase individual fitness and overall unit readiness.

The DoD substance use programs are command and medical programs that emphasize readiness and personal responsibility. These programs provide proactive services responsive to the needs of Service Members by emphasizing alcohol and other substance use deterrence, prevention, education, and rehabilitation. These substance risk reduction and prevention strategies are designed to provide effective alcohol and other substance use 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 abuse programs is to improve readiness and to restore to duty Service Members with SUD who have the potential for continued military service.

[b] Although the terminology "substance abuse" is not a diagnostic term and is not used elsewhere in the CPG, it is the language used in many DoD policies. This language is changing. For instance, the treatment portion of the Army Substance Abuse Program changed to Substance Use Disorder Clinical Care in 2016.

The Services encourage active duty Service Members who are involved in at-risk use/misuse of substances of abuse, both legal and illicit, to voluntarily refer themselves for care and treatment to a substance abuse program. However, if a Service Member screens positive for the use of illicit drugs or illegitimate use of prescription medication during a mandatory unit urinalysis, that Service Member must be evaluated for enrollment into a substance use program and begin the separation process from the military.

To effectively achieve the program goals of restoring Service Members to duty and improving readiness, the Service Member's commander must intervene early for personnel suspected of having an AUD or illicit substance use. Because many Service Members safely use alcohol, one must distinguish alcohol use from AUD. That distinction does not exist for Service Members with illicit drug use regardless of whether or not they meet criteria for SUD. Service Members who fail to participate adequately in substance use treatment or to respond successfully to rehabilitation may face administrative separation from the military. Typically, commanders separate Service Members with AUD only if they fail rehabilitation, whereas they separate Service Members with illicit drug use regardless of rehabilitation.

After enrollment into substance use programs, a treatment team (consisting of the patient, clinician, and command representative) convenes to review the treatment plan and goals. Recognizing the importance of medical readiness, HIPAA exempts communication regarding fitness for duty and military readiness between clinicians and commanders. Because substance use so directly affects readiness, this permits a significant amount of communication.

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.[c]

Mandated SUD treatment has many advantages. It allows scrutiny of Service Members with known addictions and allows commanders to separate from Service those who fail to respond to treatment before their addiction impacts mission or others in the unique military environment. And similar to treatment programs for pilots and physicians, close monitoring with the implied threat of losing one's military career discourages return to use. In addition, mandated treatment reduces attrition leading to more complete treatment with higher success rates. Finally, mandated treatment also frequently identifies other behavioral health problems, such as depression or PTSD, which require treatment.

The treatment of Service Members with SUD does not end upon separation from the military. Care of Veterans and Service Members in transition should include a transition plan that ensures continuity of care and coordination among providers. Healthcare teams should collaborate to provide assessment and services to patients throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

[c] These regulations guide the rehabilitation programs in the Services: Army Regulation 600-85, The Army Substance Abuse Program dated December 28, 2012,65. Regulation A. The Army Substance Abuse Program. 2012; OPNAVINST 5350.4D, Navy Alcohol and Drug Abuse Prevention and Control dated June 4, 2009,68. Navy Alcohol and Drug Abuse Prevention and Control, (2009); Air Force Instruction 44-121, Alcohol and Drug Abuse Prevention and Treatment (ADAPT) dated July 8, 2014.69. Alcohol and Drug Abuse Prevention and Treatment (ADAPT), (2014).

H. Substance Use Disorders and Co-occurring Conditions

a. Substance Use Disorder and Tobacco Use

The most recent DoD Health Related Behavior Survey suggests continued progress in decreasing the smoking rate among active duty personnel with rates of cigarette smoking decreasing from 24.1% in 2011 to 13.9% in 2015.(70) Comparable 2019 data from the VHA shows similar rates with 14.6% of Veterans enrolled in VHA services reporting that they currently smoke.(71) In its discussion about tobacco use disorder treatment during SUD treatment, the U.S. Substance Abuse and Mental Health Service Administration (SAMHSA) (2011) notes an early study on the morbidity and mortality among people seeking treatment for SUD.(72, 73) Among that study's 845 participants, 51% died as a result of tobacco-related causes rather than from other substance-related causes.(72)

Quitting tobacco use has clear benefits for improving 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 patient-centered care, shared decision making, and recovery.

For management of tobacco use disorder, see guidance on tobacco smoking cessation in adults from the U.S. Preventive Services Task Force (USPSTF) (https://www.uspreventiveservicestaskforce.org/uspstf/index.php/recommendation/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions) and the *Treating Tobacco Use and Dependence: 2008 Update – Clinical Practice Guideline* from the Agency for Healthcare Research and Quality (AHRQ) (https://www.ahrq.gov/prevention/guidelines/tobacco/clinicians/index.html). Also, see the most recent reports on the prevention of tobacco use from the U.S. Department of Health and Human Services: https://www.hhs.gov/surgeongeneral/reports-and-publications/tobacco/index.html, and for more information on SUD and tobacco use, see: https://www.mentalhealth.va.gov/quit-tobacco/index.asp.

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. Use of a substance should not preclude provision/continuation of guideline indicated treatment for another substance; rather, treatment should be provided for the second substance according to this CPG's recommendations. This would include effective medication treatment of OUD or AUD which should not automatically be discontinued due to a patients' use of another substance.

c. Substance Use Disorder and Other Co-occurring Conditions

For management of patients presenting with SUD and one or more of the following concerns or treatment needs, refer to the appropriate VA/DoD CPG, as available, at http://www.healthquality.va.gov/: Asthma, Chronic Insomnia Disorder and Obstructive Sleep Apnea, Chronic Kidney Disease (CKD), Chronic Multisymptom Illness (CMI), Chronic Obstructive Pulmonary Disease (COPD), Diabetes Mellitus, Headache, Hypertension, Low Back Pain (LBP), Major Depressive Disorder (MDD), Mild Traumatic Brain Injury (mTBI), Posttraumatic Stress Disorder (PTSD), Opioid Therapy for Chronic Pain, Osteoarthritis (OA), Stroke, and Suicide. As stated above, use of a substance should not automatically preclude provision/continuation of treatment for a co-occurring condition. Rather, adjustments to treatment should be made consistent with existing clinical practice guidelines, if indicated, with a focus on concurrent treatment for both concerns.

I. Overdose Education and Naloxone Distribution

Suicide and accidental overdose occur at high rates among patients with SUD in general and OUD in particular.(74) Naloxone, an opioid antagonist, can save lives when administered following an intentional or unintentional overdose on opioids, and opioid overdose education and naloxone should be offered to all patients at high risk for opioid overdose, including those with OUD.

J. Working Toward Successful Treatment of Substance Use Disorders

It is common for a person to return to use, even if his or her condition is being managed, and he or she is amenable to treatment. Returning to use does not indicate treatment has not obtained the goal; rather, it suggests it needs to be adjusted, reinstated, or changed to move toward recovery.(57) It is important to remember that "successful treatment" is unique to the individual recovering from SUD. A patient may understand success as something more than medical markers of sobriety. From a biopsychosocial perspective, examples include engagement with self, family, and society.(75) Per SAMHSA, there are 10 guiding principles of recovery, including hope, relational, person-driven, holistic, peer support, culture, addresses trauma, strengths/responsibilities, and respect.(76) Considering these while continuing to build trust with patients is imperative for successful treatment.

K. Racial and Ethnic Disparities in Care

Some studies show that racial and ethnic disparities are associated with harm regarding SUD care (in particular access to SUD care, what SUD care is offered and ultimately provided, and how long patients are retained in SUD care).(77-79) While the prevalence of SUD in the U.S. is similar (about 8%) among White, Latina/o, and Black populations, minority groups suffer more negative consequences and decreased access to evidence-based treatment and harm reduction services than others.(77, 80, 81) As an example of reported racial inequity of SUD care within VA environments, VA investigators found that access to OUD care for Veterans (e.g., buprenorphine versus methadone medication treatment) seemed to be associated with racial characteristics rather than medical, psychiatric, or service use characteristics. Moreover, VA investigators found that minorities were less likely to be retained in medication treatment.(82-84)

The Work Group acknowledges that there are other known disparities in SUD care, including gender and LGBTQ+ populations. The Work Group recognizes that data on differential access, harms, and outcomes for certain subgroups is observational. Further, the systematic evidence review did not address this and, therefore, it is outside the scope of the CPG. The Work Group notes that addressing inequity in access and outcomes of SUD care for disparate and vulnerable groups is an important topic for future research.

III. Scope of this Guideline

This CPG is based on published clinical evidence and related information available through June 30, 2020. It is intended to provide general guidance on best evidence-based practices (see Appendix A for additional information on the evidence review methodology). This CPG is not intended to serve as a standard of care.

A. Guideline Audience

This CPG is designed to assist providers (e.g., physicians, physician assistants, nurse practitioners, nurses, psychologists, social workers, pharmacists, addiction counselors, chaplains, nutritionists, dieticians, emergency care providers, behavioral health providers) in screening, assessing, and treating patients with

alcohol and substance misuse and SUD. This guideline seeks to inform providers with practical evidence-based recommendations for the most common scenarios involving patients with alcohol and substance misuse and SUD.

B. Guideline Population

The patient population of interest for this CPG is Veterans, active duty Service Members, or non-active duty Service Members ≥18 years old, as well as other adults ≥18 years old who are eligible for care in the VA and/or DoD healthcare delivery systems, who have symptoms and/or a diagnosis of SUD, including AUD, OUD, sedative hypnotic use disorder, stimulant use disorder, or cannabis use disorder. This CPG does not specifically address tobacco use disorder.

For management of tobacco use disorder, see guidance on tobacco smoking cessation in adults from the USPSTF (https://www.uspreventiveservicestaskforce.org/uspstf/index.php/recommendation/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions) and the *Treating Tobacco Use and Dependence: 2008 Update – Clinical Practice Guideline* from AHRQ (https://www.ahrq.gov/prevention/guidelines/tobacco/clinicians/index.html).

IV. Highlighted Features of this Guideline

A. Highlights in this Guideline Update

The current document is an update to the 2015 VA/DoD SUD CPG. The following significant updates make it important that providers review this version of the guideline:

- More rigorous application of Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology
- Updated algorithm for screening and treatment of SUD
- Updated algorithm for management of alcohol and opioid withdrawal syndromes
- Better definition of first- and second-line pharmacologic therapy for AUD and OUD
- Evaluated evidence regarding mindfulness-based approaches for the treatment of SUD
- Inclusion of recommendations on technology-based interventions, telephone-based care, telemedicine-delivered treatment, and computer-delivered behavioral treatments

The 2021 VA/DoD SUD CPG used stricter methodology than previous iterations. For additional information on GRADE and CPG methodology, see Appendix A.

B. Components of the Guideline

The 2021 VA/DoD SUD CPG is the 4th update to this CPG. It provides clinical practice recommendations for the care of patients with SUD (see Recommendations). In addition, the Algorithm incorporates the recommendations in the context of the flow of patient care. This CPG also includes Research Priorities, which identifies areas needing additional research.

To accompany this CPG, the Work Group also developed toolkit materials for providers and patients, including a provider summary, patient summary, and pocket card. These can be found at https://www.healthquality.va.gov/guidelines/MH/sud/.

V. Guideline Development Team

The VA Evidence Based Practice, Office of Quality and Patient Safety, in collaboration with the Clinical Quality Improvement Program, Defense Health Agency (DHA), identified the following five clinicians to serve as Champions (i.e., leaders) of this CPG's Work Group: Jennifer Burden, PhD, MS, Hildi Hagedorn, PhD, and Joseph Liberto, MD from the VA and COL Charles Milliken, MD, Ret. and COL Christopher Perry, MD from the DoD.

The Work Group comprised individuals with the following areas of expertise: dietitian, emergency medicine, family medicine, internal medicine, nursing, pain management, pharmacology, psychiatry, psychology, and social work. See Table 1 for a list of Work Group members.

This CPG Work Group, led by the Champions, was tasked with:

- Determining the scope of the CPG
- Crafting clinically relevant key questions (KQs) to guide the systematic evidence review
- Identifying discussion topics for the patient focus group and considering the patient perspective
- Providing direction on inclusion and exclusion criteria for the systematic evidence review and the assessment of the level and quality of evidence
- Developing evidence-based clinical practice recommendations, including determining the strength and category of each recommendation

The Lewin Team, including The Lewin Group, ECRI, Sigma Health Consulting, Duty First Consulting, and Anjali Jain Research & Consulting was contracted by the VA to help develop this CPG.

Table 1. Guideline Work Group and Guideline Development Team

Organization	Name*
Department of Veterans Affairs	**Jennifer Burden, PhD, MS (Champion)**
	Hildi Hagedorn, PhD (Champion)
	Joseph Liberto, MD (Champion)
	Timothy Atkinson, PharmD
	Adam J. Gordon, MD, MPH
	James McKay, PhD
	Larissa Mooney, MD
	Renee Redden, PMHCNS, BC
	Renada Rochon, DNP, RN
	Comilla Sasson, MD, PhD
	Andrew Saxon, MD

Organization	Name*
Department of Defense	**COL Charles Milliken, MD, Ret. (Champion)**
	COL Christopher Perry, MD (Champion)
	Charolotte Baldridge, FNP
	Rachael Coller, PharmD, BCPS, BCPP
	Christopher Spevak, MD, MPH, JD
	Kathleen Stack, MD
	MAJ Christopher Taylor, MD
Office of Quality and Patient Safety Veterans Health Administration	M. Eric Rodgers, PhD, FNP-BC
	James Sall, PhD, FNP-BC
	Rene Sutton, BS, HCA
Clinical Quality Improvement Program Defense Health Agency	Lisa D. Jones, BSN, RN, MHA, CPHQ
	Corinne K. B. Devlin, MSN, RN, FNP-BC
	Elaine Stuffel, MHA, BSN, RN
	Katherine E. Taylor-Pearson, DNP, RN-BC, CNE, CLSSBB
The Lewin Group	Clifford Goodman, PhD
	Erika Beam, MS
	Ben Agatston, JD, MPH
	Andrea Dressel, BS
	Evelyn Nkooyooyo, BA
ECRI	Kris D'Anci, PhD
	Stacey Uhl, MS
	Linnea Hermanson, MA
	Amber Moran, MA
	Aaron Bloschichak, MPH
	Pasqualina Santaguida, PhD
	Kristina McShea, MSLIS
	Megan S. Nunemaker, MSLS
Anjali Jain Research & Consulting	Anjali Jain, MD
Sigma Health Consulting	Frances Murphy, MD, MPH
	James Smirniotopoulos, MD
Duty First Consulting	Rachel Piccolino, BA
	Mary Kate Curley, BA

*Additional contributor contact information is available in Appendix I.

VI. Summary of Guideline Development Methodology

The methodology used in developing this CPG follows the *Guideline for Guidelines*, an internal document of the VA and DoD EBPWG updated in January 2019 that outlines procedures for developing and submitting VA/DoD CPGs.(85) The *Guideline for Guidelines* is available at http://www.healthquality.va.gov/policy/index.asp. This CPG also aligns with NAM's principles of trustworthy CPGs (e.g., explanation of evidence quality and strength, the management of potential

conflicts of interest [COI], interdisciplinary stakeholder involvement, use of systematic review, and external review).(86) Appendix A provides a detailed description of the CPG development methodology.

A. Evidence Quality and Recommendation Strength

The Work Group used the GRADE approach to craft each recommendation and determine its strength. Per GRADE approach, recommendations must be evidence-based and cannot be made based on expert opinion alone. The GRADE approach uses the following four domains to inform the strength of each recommendation (see Grading Recommendations):(87)

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

Using these four domains, the Work Group determined the relative strength of each recommendation (*Strong* or *Weak*). 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 incorporates the four domains.(88) A *Strong* recommendation generally indicates *High* or *Moderate* confidence in the quality of the available evidence, a clear difference in magnitude between the benefits and harms of an intervention, similar patient values and preferences, and understood influence of other implications (e.g., resource use, feasibility).

In some instances, there is insufficient evidence on which to base a recommendation for or against a particular therapy, preventive measure, or other intervention. For example, the systematic evidence review may have found little or no relevant evidence, inconclusive evidence, or conflicting evidence for the intervention. The manner in which this is expressed in the CPG may vary. In such instances, the Work Group may include among its set of recommendations an insufficient evidence statement for an intervention that may be in common practice even though it is not supported by clinical evidence, and particularly if there may be other risks of continuing to use it (e.g., high opportunity cost, misallocation of resources). In other cases, the Work Group may decide not to include this type of statement about an intervention. For example, the Work Group may remain silent where there is an absence of evidence for a rarely used intervention. In other cases, an intervention may have a favorable balance of benefits and harms but may be a standard of care for which no recent evidence has been generated.

Using these elements, the Work Group determines the strength and direction of each recommendation and formulates the recommendation with the general corresponding text (see Table 2).

Table 2. Strength and Direction of Recommendations and General Corresponding Text

Recommendation Strength and Direction	General Corresponding Text
Strong for	We recommend …
Weak for	We suggest …
Neither for nor against	There is insufficient evidence to recommend for or against …
Weak against	We suggest against …
Strong against	We recommend against …

It is important to note that a recommendation's strength (i.e., *Strong* versus *Weak*) is distinct from its clinical importance (e.g., a *Weak* recommendation is evidence-based and still important to clinical care). The strength of each recommendation is shown in the Recommendations section.

This CPG's use of GRADE reflects a more rigorous application of the methodology than previous iterations. For instance, the determination of the strength of the recommendation is more directly linked to the confidence in the quality of the evidence on outcomes that are critical to clinical decision-making. The confidence in the quality of the evidence is assessed using an objective, systematic approach that is independent of the clinical topic of interest. Therefore, recommendations on topics for which it may be inherently more difficult to design and conduct rigorous studies (e.g., RCTs) are typically supported by lower quality evidence and, in turn, *Weak* recommendations. Recommendations on topics for which rigorous studies can be designed and conducted may more often be *Strong* recommendations. Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(89, 90) This stricter standard provides a consistent approach to determining recommendation strengths. For additional information on GRADE or CPG methodology, see Appendix A.

B. Categorization of 2015 Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current. Except for an original version of a new CPG, this typically requires revision of a CPG's previous versions based on new evidence or as scheduled subject to time-based expirations.(91) For example, the USPSTF has a process for monitoring the emergence of new evidence that could prompt an update of its recommendations, and it aims to review each topic at least every five years for either an update or reaffirmation.(92)

Recommendation categories were used to track how the previous CPG's recommendations could be reconciled. These categories and their corresponding definitions are similar to those used by the National Institute for Health and Care Excellence (NICE, England).(93, 94) Table 3 lists these categories, which are based on whether the evidence supporting a recommendation was systematically reviewed, the degree to which the previous CPG's recommendation was modified, and whether a previous CPG's recommendation is relevant in the updated CPG.

Additional information regarding these categories and their definitions can be found in Recommendation Categorization. The 2021 CPG recommendation categories can be found in Recommendations. Appendix E outlines the 2015 VA/DoD SUD CPG's recommendation categories.

Table 3. Recommendation Categories and Definitions[a]

Evidence Reviewed	Recommendation Category	Definition
Reviewed[b]	New-added	New recommendation
	New-replaced	Recommendation from previous CPG was carried forward and revised
	Not changed	Recommendation from previous CPG was carried forward but not changed
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted
Not reviewed[c]	Not changed	Recommendation from previous CPG was carried forward but not changed
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted

[a] Adapted from the NICE guideline manual (2012) (93) and Garcia et al. (2014) (94)

[b] The topic of this recommendation was covered in the evidence review carried out as part of the development of the current CPG.

[c] The topic of this recommendation was not covered in the evidence review carried out as part of the development of the current CPG.

Abbreviations: CPG: clinical practice guideline

C. Management of Potential or Actual Conflicts of Interest

Management of COIs for the CPGs is conducted as described in the *Guideline for Guidelines*.(85) Further, the *Guideline for Guidelines* refers to details in the VHA Handbook 1004.07 Financial Relationships between VHA Health Care Professionals and Industry (November 2014, issued by the VHA National Center for Ethics in Health Care),(95) as well as to disclosure statements (i.e., the standard disclosure form that is completed at least twice by CPG Work Group members and the guideline development team).(85) The disclosure form inquires regarding any relevant financial and intellectual interests or other relationships with, e.g., manufacturers of commercial products, providers of commercial services, or other commercial interests. The disclosure form also inquires regarding any other relationships or activities that could be perceived to have influenced, or that give the appearance of potentially influencing, a respondent's contributions to the CPG. In addition, instances of potential or actual COIs among the CPG Work Group and the guideline development team were also subject to random web-based identification via standard electronic means (e.g., Centers for Medicare & Medicaid Services Open Payments and/or ProPublica).

Potential COIs were reported to the VA and DoD program offices and reviewed with the Champions. The VA and DoD program offices and the Champions determined further action as appropriate (e.g., excusing Work Group members from selected relevant deliberations). Disclosure forms are on file with the VA Office of Quality and Patient Safety and are available upon request.

D. Patient Perspective

When developing a CPG, consideration should be given to patient perspectives and experiences, which often vary from those of providers.(89, 96) Focus groups can be used to help collect qualitative data on patient perspectives and experiences. VA and DoD Leadership arranged a virtual patient focus group on April 29, 2020. The focus group aimed to gain insights into patients with SUD of potential relevance and incorporate these into the CPG as appropriate. Topics discussed included the patients' priorities,

challenges they have experienced, information they have received regarding their care, and the impacts of their care on their lives.

The patient focus group comprised a convenience sample of eight people. There were six males and two females. Five participants were Veterans who received care from the VA health system, and three participants received care from the DoD health system (one of which was an active duty Service Member). The Work Group acknowledges this convenience sample is not representative of all patients with SUD within the VA and DoD healthcare systems and, thus, findings are not generalizable and do not comprise evidence. For more information on the patient focus group methods and findings, see Appendix F. Patient focus group participants were provided the opportunity to review the final draft and provide additional feedback.

E. External Peer Review

The Work Group drafted, reviewed, and edited this CPG using an iterative process. For more information, see Drafting and Finalizing the Guideline. Once the Work Group completed a near-final draft, they identified experts from the VA and DoD healthcare systems and outside organizations to review that draft. The draft was sent to those experts for a 14-business-day review and comment period. The Work Group considered all feedback from the peer reviewers and modified the CPG where justified, in accordance with the evidence. The organizations that provided feedback on this CPG include: American Academy of Addiction Psychiatry, SAMHSA, and the University of Hawai'i.

F. Implementation

This CPG and algorithm are designed to be adapted by individual healthcare providers with consideration of unique patient considerations and preferences, local needs, and resources. The algorithm serves as a tool to prompt providers to consider key decision points in the care for a patient with SUD. The Work Group submits suggested performance metrics for the VA and DoD to use when assessing the implementation of this CPG. Robust implementation is identified within VA and DoD internal implementation plans and policies. Additionally, implementation would entail wide dissemination through publication in the medical literature, online access, educational programs, and, ideally, electronic medical record (EMR) programming in the form of clinical decision support tools at the point of care.

VII. Approach to Care in Department of Veterans Affairs and Department of Defense

A. Patient-centered Care

Guideline recommendations are intended to consider patient needs and preferences and represent a whole/holistic health approach to care that is patient-centered, culturally appropriate, and available to people with limited literacy skills and physical, sensory, or learning disabilities. VA/DoD CPGs encourage providers to use a patient-centered, whole health/holistic health approach (i.e., individualized treatment based on patient needs, characteristics, goals, and preferences). This approach aims to treat the particular condition while also optimizing the individual's overall health and well-being.

Regardless of the care setting, all patients should have access to individualized, evidence-based care. Patient-centered care can decrease patient anxiety, increase trust in clinicians, and improve treatment

adherence.(97, 98) A whole/holistic health approach (https://www.va.gov/wholehealth/) empowers and equips individuals to meet their personal health and well-being goals. Good communication is essential and should be supported by evidence-based information tailored to each patient's needs. An empathetic and non-judgmental approach facilitates discussions sensitive to gender, culture, ethnicity, socioeconomic, and other differences.

As part of patient-centered care, SUD care is moving toward a stepped-care approach. This means that care for SUD should not be restricted to SUD specialty care environments, but should be provided in the setting that best matches the patient's needs and preferences. Ideal care for patients with heavy or risky drinking, for example, is to view the disorder on a continuum, and identify risky drinking and subsequently intervene in the primary care setting before it progresses to AUD. In addition, VHA has provided medication for OUD in primary care, pain management, and general mental health clinics utilizing a stepped care approach.

In short, patients with mild SUD can be appropriately managed in primary care settings. In addition, patients with more severe SUD who are not willing to follow through with a referral to specialty SUD care due to stigma may also be treated in settings outside SUD specialty care. Providers in other settings can assist these patients with medication therapy (when appropriate) and motivational approaches to encourage involvement with SUD specialty care. Consultation with SUD specialty care providers can assist providers in other settings with the management of these patients.

B. Shared Decision Making

This CPG encourages providers to practice shared decision making. Shared decision making was emphasized in *Crossing the Quality Chasm,* an IOM report, in 2001.(99) Providers must be adept at presenting information to their patients regarding individual treatments, expected risks, expected outcomes, and levels and/or settings of care, especially where there may be patient heterogeneity in risks and benefits. The VHA and MHS have embraced shared decision making. Providers are encouraged to use shared decision making to individualize treatment goals and plans based on patient capabilities, needs, and preferences.

C. Patients with Co-occurring Conditions

Co-occurring conditions can modify the degree of risk, impact diagnosis, influence patient and provider treatment priorities and clinical decisions, and affect the overall approach to the management of SUD. Many Veterans, Service Members, and their families have one or more co-occurring conditions. Because SUD is sometimes accompanied by co-occurring conditions, it is best to provide integrated care for all conditions in a single setting when possible, and if not, SUD should be managed collaboratively. Some co-occurring conditions may require early specialist consultation to determine any necessary changes in treatment or to establish a common understanding of how care will be coordinated. This may entail referral to other VA/DoD CPGs (e.g., Asthma, Chronic Insomnia Disorder and Obstructive Sleep Apnea, CKD, CMI, COPD, Diabetes Mellitus, Headache, Hypertension, LBP, MDD, mTBI, PTSD, Opioid Therapy for Chronic Pain, OA, Stroke, and Suicide[d]).

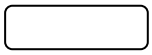
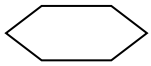
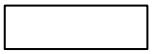
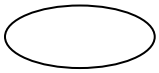
[d] See all the VA/DoD Clinical Practice Guidelines available at: https://www.healthquality.va.gov/guidelines/

VIII. Algorithm

This CPG's algorithm is designed to facilitate understanding of the clinical pathway and decision making process used in managing patients with SUD. This algorithm format represents a simplified flow of the management of patients with SUD and helps foster efficient decision making by providers. It includes:

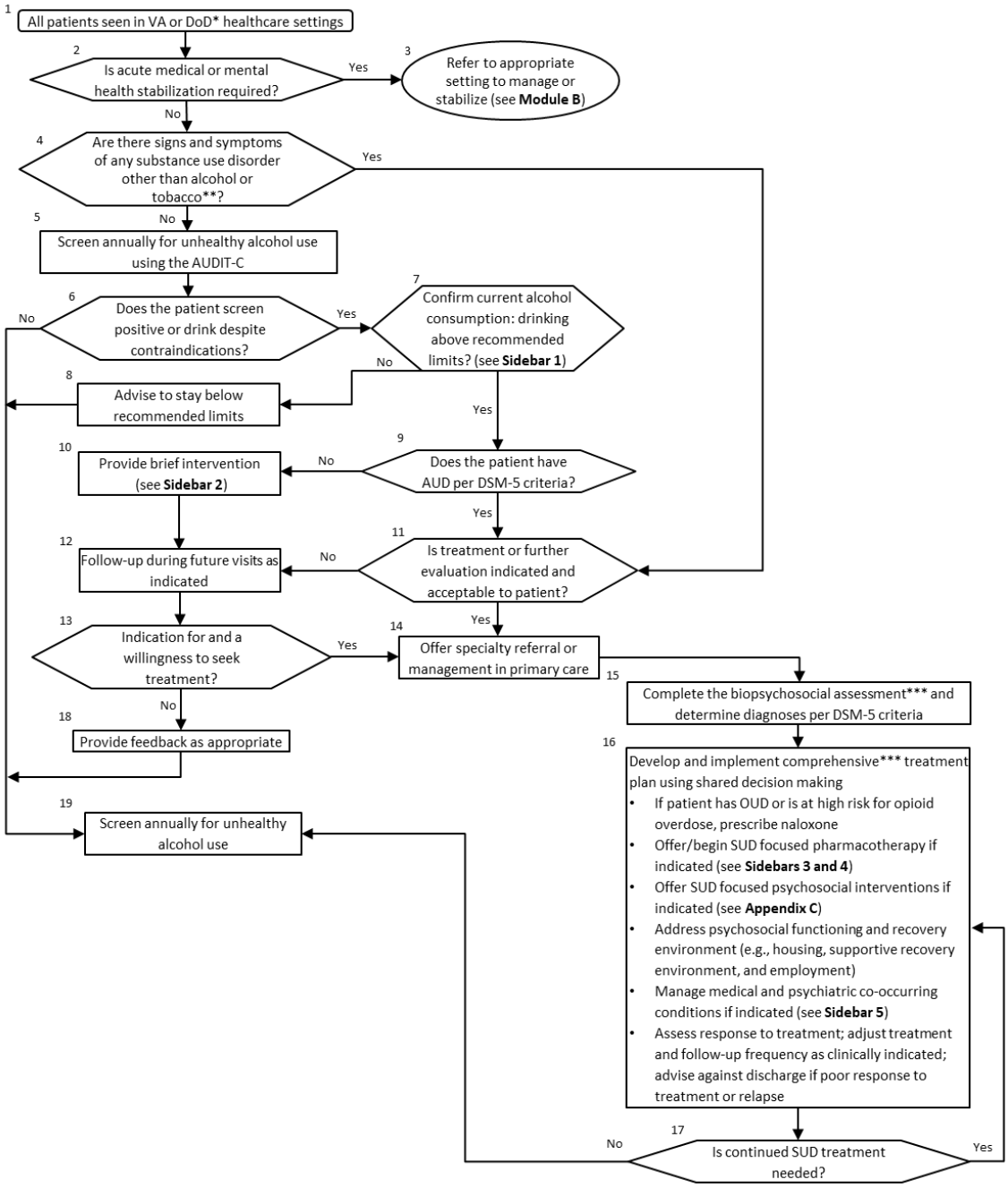
- An ordered sequence of steps of care
- Decisions to be considered
- Recommended decision criteria
- Actions to be taken

The algorithm is a step-by-step decision tree. Standardized symbols are used to display each step, and arrows connect the numbered boxes indicating the order in which the steps should be followed.(100) Sidebars provide more detailed information to assist in defining and interpreting elements in the boxes.

Shape	Description
	Rounded rectangles represent a clinical state or condition
	Hexagons represent a decision point in the process of care, formulated as a question that can be answered "Yes" or "No"
	Rectangles represent an action in the process of care
	Ovals represent a link to another section within the algorithm

Appendix G contains alternative text descriptions of the algorithm modules.

A. Module A: Screening and Treatment



* 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, see guidance on tobacco smoking cessation in adults from the USPSTF (https://www.uspreventiveservicestaskforce.org/uspstf/index.php/recommendation/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions) and the *Treating Tobacco Use and Dependence: 2008 Update – Clinical Practice Guideline* from AHRQ (https://www.ahrq.gov/prevention/guidelines/tobacco/clinicians/index.html).

*** Specific to specialty care setting

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, 5th edition; DoD: Department of Defense; OUD: opioid use disorder; SUD: substance use disorders; VA: Department of Veterans Affairs

Sidebar 1: Recommended Limits for Alcohol Consumption[a]
Men age 65 or below: ≤2 standard drinks per day on average; ≤4 drinks on any one day; ≤14 drinks per week
Men over age 65 and all women: ≤1 standard drink per day on average; ≤3 drinks on any one day; ≤7 drinks per week
Patients with contraindications including potential drug-drug interactions: 0 standard drinks per day

[a] For more information on recommended limits for alcohol consumption, please see: https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking and https://www.dietaryguidelines.gov/resources/2020-2025-dietary-guidelines-online-materials. Please note the above limits are adapted from these sources.

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: naltrexone, topiramate
Suggested: acamprosate, disulfiram
Suggested as second line: gabapentin
Opioid Use Disorder
Recommended: buprenorphine/naloxone, methadone
Suggested: extended-release naltrexone

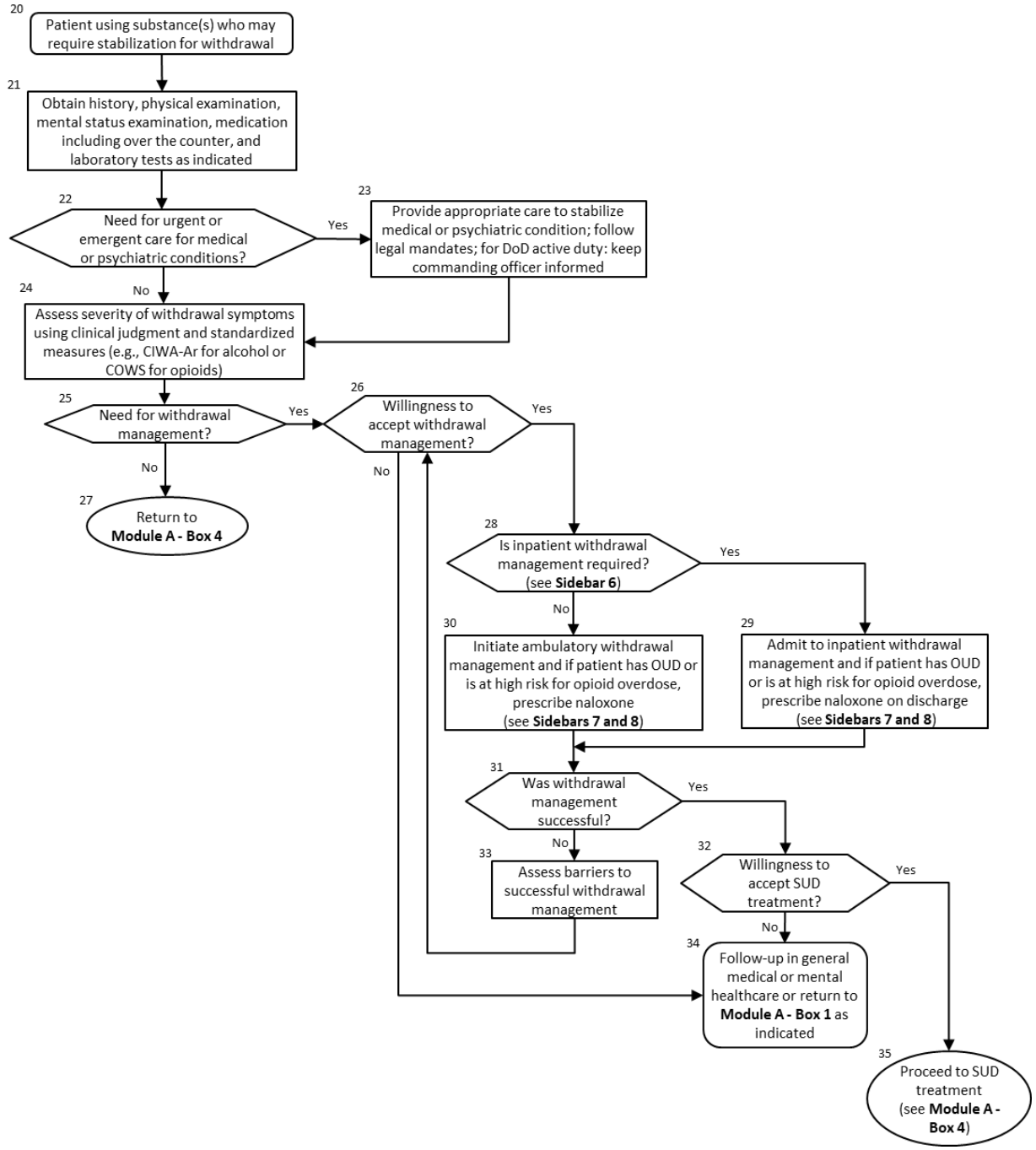
Sidebar 4: Components of Addiction-focused Medical Management
• Monitoring adherence, response to treatment, and adverse effects
• Education about AUD/OUD, health consequences, and treatments
• Encouragement to abstain from illicit opioids and other addictive substances
• Encouragement to attend and referral to community supports for recovery
• Encouragement to make lifestyle changes that support recovery

Abbreviations: AUD: alcohol use disorder; OUD: opioid use disorder

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., Asthma, Chronic Insomnia Disorder and Obstructive Sleep Apnea, CKD, CMI, COPD, Diabetes Mellitus, Headache, Hypertension, LBP, MDD, mTBI, PTSD, Opioid Therapy for Chronic Pain, Osteoarthritis, Stroke, and Suicide)

Abbreviations: CKD: Chronic Kidney Disease; CMI: Chronic Multisymptom Illness; COPD: Chronic Obstructive Pulmonary Disease; CPG: clinical practice guideline; DoD: Department of Defense; LBP: Low Back Pain; MDD: Major Depressive Disorder; mTBI: Mild Traumatic Brain Injury; PTSD: Posttraumatic Stress Disorder; SUD: substance use disorders; VA: Department of Veterans Affairs

B. Module B: Stabilization and Withdrawal



Abbreviations: CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol-Revised; COWS: Clinical Opiate Withdrawal Scale; DoD: Department of Defense; OUD: opioid use disorder; SUD: substance use disorders

Sidebar 6: Treatment Setting for Alcohol Withdrawal

Inpatient medically supervised alcohol withdrawal management is strongly supported by expert consensus for patients with symptoms of severe alcohol withdrawal (i.e., CIWA-Ar score ≥20) or patients with:

- 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
- Risk of withdrawal from other substances in addition to alcohol (e.g., sedative hypnotics)
- Moderate alcohol withdrawal (i.e., CIWA-Ar score ≥10) and any of the following:
  - 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

Abbreviations: CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol-Revised

Sidebar 7: Pharmacologic Treatment

Alcohol Withdrawal

For managing moderate-severe alcohol withdrawal: Benzodiazepines

For patients without severe alcohol withdrawal for whom risks of benzodiazepines outweigh benefits:

- Carbamazepine
- Gabapentin
- Valproic acid

Opioid Withdrawal

For patients with OUD for whom maintenance agonist treatment is contraindicated, unacceptable, or unavailable, we recommend a taper using:

- Buprenorphine
- Methadone in inpatient or OTP only

For patients with OUD for whom methadone and/or buprenorphine are contraindicated, unacceptable, unavailable, or for whom extended-release injectable naltrexone is planned: Lofexidine or clonidine

Abbreviations: OTP: Opioid Treatment Program; OUD: opioid use disorder

Sidebar 8: Tapering Strategies

Alcohol Withdrawal (use one of the following)

- 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., PRN dosing)

Opioid Withdrawal

- Use structured taper for methadone and buprenorphine

Abbreviations: PRN: as needed

IX. Recommendations

The following evidence-based clinical practice recommendations were made using a systematic approach considering four domains as per the GRADE approach (see Summary of Guideline Development Methodology). These domains include: confidence in the quality of the evidence, balance of desirable and undesirable outcomes (i.e., benefits and harms), patient values and preferences, and other implications (e.g., resource use, equity, acceptability).

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Screening and Brief Alcohol Intervention		1.	For patients in general medical and mental healthcare settings, we recommend screening for unhealthy alcohol use periodically using the three-item Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) or Single Item Alcohol Screening Questionnaire (SASQ).	Strong for	Not reviewed, Amended
		2.	For patients without documented alcohol use disorder who screen positive for unhealthy alcohol use, we suggest providing a single initial brief intervention regarding alcohol-related risks and advising to abstain or drink within established limits for daily and weekly consumption.	Weak for	Not reviewed, Amended
		3.	There is insufficient evidence to recommend for or against screening for drug use disorders in primary care to facilitate enrollment in treatment.	Neither for nor against	Reviewed, New-added
Treatment Setting		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.	Neither for nor against	Not reviewed, Amended
Stabilization and Withdrawal	***a. Alcohol Use Disorder***	5.	For the treatment of moderate-severe alcohol withdrawal, we recommend using benzodiazepines with adequate monitoring.	Strong for	Not reviewed, Amended
		6.	For managing mild-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	Not reviewed, Not changed

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Stabilization and Withdrawal (cont.)	*b. Opioid Use Disorder*	7.	For patients with opioid use disorder, we recommend against withdrawal management, without planned ongoing pharmacotherapy treatment, due to high risk of relapse and overdose (see Recommendations 16, 17, and 18).	Strong against	Not reviewed, Amended
		8.	For patients with opioid use disorder for whom opioid withdrawal management is indicated, we suggest using: • Buprenorphine/naloxone (in any setting); or • Methadone or buprenorphine/naloxone (in inpatient or accredited Opioid Treatment Programs) (see Recommendation 17).	Weak for	Reviewed, New-replaced
		9.	For patients with opioid use disorder for whom withdrawal management is indicated and for whom methadone and buprenorphine are contraindicated, unacceptable, or unavailable, we suggest offering clonidine or lofexidine as a second-line agent for opioid withdrawal management (see Recommendation 17).	Weak for	Reviewed, New-replaced
	c. Sedative Hypnotic Use Disorder	10.	For patients in need of withdrawal management for benzodiazepines, we recommend gradually tapering benzodiazepines.	Strong for	Reviewed, New-replaced
		11.	There is insufficient evidence to recommend the use of adjunctive medications for the treatment of benzodiazepine withdrawal.	Neither for nor against	Reviewed, New-added
Treatment	*a. Alcohol Use Disorder — Pharmacotherapy*	12.	For patients with moderate-severe alcohol use disorder, we recommend offering one of the following medications: • Naltrexone (oral or extended-release) • Topiramate	Strong for	Not reviewed, Amended
		13.	For patients with moderate-severe alcohol use disorder, we suggest offering one of the following medications: • Acamprosate • Disulfiram	Weak for	Not reviewed, Amended
		14.	For patients with moderate-severe alcohol use disorder for whom first-line pharmacotherapy is contraindicated or ineffective, we suggest offering gabapentin.	Weak for	Not reviewed, Not changed
	b. Alcohol Use Disorder – Psychosocial Interventions	15.	For patients with alcohol use disorder, we suggest one or more of the following interventions, considering patient preference and availability: • Behavioral couples therapy • Cognitive behavioral therapy • Community reinforcement approach • Motivational enhancement therapy • 12-step facilitation	Weak for	Not reviewed, Amended

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Treatment (cont.)	*c. Opioid Use Disorder – Pharmacotherapy*	16.	For patients with opioid use disorder, we recommend one of the following strategies: • Buprenorphine/naloxone in any setting; or • Methadone or buprenorphine/naloxone provided through an accredited Opioid Treatment Program	Strong for	Reviewed, Amended
		17.	For patients with opioid use disorder, we suggest offering extended-release naltrexone (IM).	Weak for	Reviewed, New-replaced
		18.	There is insufficient evidence to recommend any one of the different FDA-approved formulations or routes of delivery of buprenorphine over another.	Neither for nor against	Reviewed, New-added
		19.	There is insufficient evidence to recommend for or against oral naltrexone for the treatment of opioid use disorder.	Neither for nor against	Reviewed, Not changed
	d. Opioid Use Disorder – Psychosocial Interventions	20.	For patients receiving medication treatment for opioid use disorder, there is insufficient evidence to recommend for or against any specific psychosocial interventions in addition to addiction-focused medical management.	Neither for nor against	Reviewed, Amended
		21.	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.	Neither for nor against	Not reviewed, Amended
	e. Cannabis Use Disorder – Pharmacotherapy	22.	There is insufficient evidence to recommend for or against the use of pharmacotherapy in the treatment of cannabis use disorder.	Neither for nor against	Reviewed, Not changed
	f. Cannabis Use Disorder – Psychosocial Interventions	23.	For patients with cannabis use disorder, we suggest one of the following interventions as initial treatment, considering patient preference and availability: • Cognitive behavioral therapy • Motivational enhancement therapy • Combined cognitive behavioral therapy/motivational enhancement therapy	Weak for	Reviewed, Amended
		24.	We suggest against the use of a brief intervention (i.e., 60 minutes or less) for the treatment of cannabis use disorder.	Weak against	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Treatment (cont.)	*g. Stimulant Use Disorder – Pharmacotherapy*	25.	There is insufficient evidence to recommend for or against the use of any pharmacotherapy for the treatment of cocaine use disorder or amphetamine/methamphetamine use disorder.	Neither for nor against	Reviewed, Amended
	h. Stimulant Use Disorder – Psychosocial Interventions	26.	For patients with cocaine use disorder, we recommend one or more of the following interventions as initial treatment, considering patient preference and availability: • Cognitive behavioral therapy • Recovery-focused behavioral therapy (i.e., individual drug counseling and community reinforcement approach) • Contingency management in combination with another behavioral intervention considering patient preference and availability	Strong for	Not reviewed, Amended
		27.	For patients with amphetamine/methamphetamine use disorder, we suggest offering contingency management as initial treatment in combination with another behavioral intervention, considering patient preference and availability.	Weak for	Not reviewed, Amended
Group Mutual Help Involvement		28.	For patients with alcohol use disorder 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 availability: • Peer linkage • Network support • 12-step facilitation	Strong for	Reviewed, New-replaced
		29.	For patients with drug use disorders in early recovery or following relapse, we suggest promoting active involvement in group mutual help programs using one of the following systematic approaches, considering patient preference and availability: • Peer linkage • 12-step facilitation	Weak for	Reviewed, New-replaced
Mindfulness-based Therapies		30.	There is insufficient evidence to recommend for or against mindfulness-based therapies for the treatment of substance use disorders.	Neither for nor against	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Telehealth		31.	We suggest using technology-based interventions (e.g., automated text/voice messaging, smartphone apps), in addition to usual care, for alcohol use disorder.	Weak for	Reviewed, New-added
		32.	There is insufficient evidence to recommend for or against using technology-based interventions (e.g., automated text/voice messaging, smartphone apps), in addition to usual care, for substance use disorders other than alcohol use disorder.	Neither for nor against	Reviewed, New-added
		33.	We suggest the use of structured telephone-based care as an adjunct to usual care for substance use disorders.	Weak for	Reviewed, New-added
		34.	There is insufficient evidence to recommend for or against the use of telemedicine-delivered treatment for substance use disorders.	Neither for nor against	Reviewed, New-added
		35.	There is insufficient evidence to recommend for or against the use of computer-delivered behavioral treatments, either alone or in combination with usual care, for substance use disorders.	Neither for nor against	Reviewed, New-added

[a] For additional information, see Grading Recommendations.

[b] For additional information, see Recommendation Categorization.

A. Screening and Brief Alcohol Intervention

Recommendation

1. For patients in general medical and mental healthcare settings, we recommend screening for unhealthy alcohol use periodically 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

Periodic screening for unhealthy alcohol use is recommended for all patients based on moderate to high quality evidence that alcohol screening followed by brief alcohol counseling is efficacious for reducing drinking among individuals who do not meet DSM-5 criteria for AUD.(101, 102) Screening should identify patients along the entire continuum of unhealthy alcohol use including those who drink above recommended limits (i.e., risky or hazardous drinking) and those with severe AUD.

Most screen-positive patients will not have AUD and should not be given a diagnosis solely based on screening results; this has particular importance in the DoD setting where a diagnosis of AUD may limit assignment selection or have other career consequences. Most screen-positive patients will be appropriate candidates for brief alcohol counseling as the initial treatment approach for unhealthy alcohol use.(102)

One of two validated brief screens is recommended to identify past-year unhealthy alcohol use: the AUDIT-C (103-106) or a single item alcohol screen for drinking above recommended daily limits (SASQ).(107) More information on the AUDIT-C and SASQ can be found in Table 4. The AUDIT-C may be preferable in the following situations:

- When there is a specific service requirement (i.e., VA or DoD quality indicators)
- When an EMR can score the AUDIT-C and provide decision support to the provider
- When the clinician preference is to obtain information regarding:
  - Any drinking (for those with contraindications)
  - Typical drinking (for medication interactions)
  - Episodic heavy drinking
  - AUDIT-C scores have predictive validity for alcohol-related health outcomes (108-110)

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

Table 4. 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?*	Never	0 point	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?
		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 (for men) or 4 or more (for women) 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. VA and DoD currently consider a screen positive for unhealthy alcohol use if AUDIT-C score is ≥5 points.			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.

Note: The Work Group notes that this subject is actively evolving; the information presented here is current in March 2021. For VA patients and providers, documentation of brief alcohol counseling is required for those with AUDIT-C ≥5 points, for men and women. Similar guidance is being included in DoD's updated EMR. This higher AUDIT-C score was selected to minimize the false-positive rate and to target implementation efforts. Follow-up of screening scores <5 is left to provider discretion. A "positive AUDIT-C" should never be the sole criterion for entering an alcohol diagnosis into the EMR. Further, within DoD, such a diagnosis may limit future roles and thus further exacerbate existing stigma surrounding alcohol use. For more information, see Hoggatt et al. (2018) "Brief Report: Identifying Women Veterans With Unhealthy Alcohol Use Using Gender-Tailored Screening."(111)

Abbreviations: AUDIT-C: Alcohol Use Disorders Identification Test – Consumption; DoD: Department of Defense; SASQ: Single-Item Alcohol Screening Questionnaire; VA: Department of Veterans Affairs.

As highlighted in the IOM review of substance use in the DoD,(31) there is considerable stigma among Service Members regarding a possible alcohol diagnosis impacting their military career; understandably, this may impact screening effectiveness. Policies like the recent Army Directive (2019-12) (49) may improve screening effectiveness and should be considered for implementation across the DoD as recommended by the IOM.(31) The Army Directive policy allows alcohol diagnosis and care that does not require notification of Command authorities or mandatory treatment (both of which may impact military careers) in most cases when the soldier voluntarily seeks care. Further DoD research is needed on policies surrounding diagnosis and treatment for Service Members who seek care voluntarily.

Additional DoD research should also examine whether it is preferable to administer the annual AUDIT-C in a "medical readiness clinic" or a Service Member's primary care clinic since the VA and DoD have imbedded behavioral health providers in primary care, which may also improve the availability or effectiveness of brief interventions (BI) or brief treatment referrals in that setting. More research is also

needed on the optimal frequency of screening for unhealthy alcohol use (112, 113) and alternative methods to promote more efficient and accurate collection of screening data directly from patients.(114)

As this is a *Not reviewed, Amended* recommendation, the Work Group considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(101, 102) The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had limitations in the methodological quality, the size of the included randomized controlled trials (RCTs), and attrition rate. The benefits (e.g., importance of screening for unhealthy alcohol use) outweighed the potential harms (e.g., extra time taken by patients and providers). Patient values and preferences vary somewhat because Service Members with unhealthy alcohol use in the Army can voluntarily receive treatment without serious career implications, but those in other services cannot. Veterans may also have varied values and preferences due to comfort levels with screening. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

2. For patients without documented alcohol use disorder who screen positive for unhealthy alcohol use, we suggest providing a single initial brief intervention regarding alcohol-related risks and advising to abstain or drink within established limits for daily and weekly consumption.
   (Weak for | Not reviewed, Amended)

Discussion

The VA and DoD currently consider a screen positive for unhealthy alcohol use if the AUDIT-C score is ≥5 points or if the SASQ score is positive (however, a provider may still choose to discuss drinking habits with a patient who scores <5 on the AUDIT-C).

Based on several SRs, the Work Group suggests a single BI for adults who screened positive for unhealthy alcohol use.(102, 115) These SRs present low to moderate quality evidence for the efficacy of a BI in reducing consumption outcomes and improving certain health outcomes. The Work Group determined the benefits outweighed harms among those with unhealthy alcohol use who do not meet diagnostic criteria for AUD. At the provider's discretion, individuals who are at 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 and managed per 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.(102, 115) Based on this finding, and to reduce the risk of multiple sessions of BI delaying or diverting medical resources that might have been used to address more pressing concerns, we suggest a single initial BI. Providers may offer follow-up BIs as clinically indicated, based on additional independent risk factors and co-occurring conditions.

Similarly, there is no evidence to suggest a difference in efficacy between 5, 10, or 20-minute interventions (116, 117) or that certain components of BIs are more effective than others. Two BI elements that consistently show benefit in RCTs 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.(102, 115) Providers can also discuss the benefits of reducing alcohol consumption and effective strategies for doing so. Motivational interviews focused on

supporting patients in choosing their drinking goal when ready to make a change may be effective 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 number of 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. Low quality evidence showed similar decreases in alcohol consumption outcomes in female-only trials, in pregnant women, and Veterans. The health outcomes improved with BIs were all-cause mortality, hospitalization rates, and systolic blood pressure.

Brief interventions were effective for adults with unhealthy alcohol use who do not have AUD in various clinical settings (e.g., primary care, emergency department [ED], hospital settings). Evidence also shows BIs are effective when provided by primary care providers, nurses, psychologists, or health educators. Therefore, various providers can administer BIs if it is within their scope of practice and facility privileges.

Despite the potentially significant time investment (five minutes in a 20-minute primary care visit), the benefits of BIs outweigh the harms since BI may decrease alcohol consumption. There may be slight variation in patient preferences due to initial resistance to intervention, but most patients are relatively open to listening to BI and MI techniques.

As this is a *Not reviewed, Amended* recommendation, the Work Group considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(102, 115-117) The Work Group downgraded the strength of the recommendation from the 2015 VA/DoD SUD CPG due to the low quality evidence for several critical outcomes. The benefits outweighed the harms of BI for adults with risky alcohol use without a diagnosis of AUD, and there is some variation in patient preferences. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

3. There is insufficient evidence to recommend for or against screening for drug use disorders in primary care to facilitate enrollment in treatment.
   (Neither for nor against | Reviewed, New-added)

Discussion

Evidence suggests screening for drug use disorders does not significantly increase enrollment into treatment programs. The only study reviewed, Richards et al. (2019), found implementation of a standardized screening tool for drug use disorders could identify a significantly higher number of individuals with cannabis use disorder; however, this did not increase enrollment in treatment programs.(118)

Stigma surrounding drug use disorders complicates care since identifying a drug use disorder does not increase the likelihood of enrollment in treatment. Further, time is limited since primary care appointments in the VA/DoD are generally limited to 20 minutes. This forces providers to choose between utilizing a tool that may identify a drug use disorder or focusing on more actionable healthcare concerns.

There is some variation in patient preferences regarding screening for drug use disorders. Veterans may be offended by drug use disorder screening or may seem ambivalent to the process. Conversely, DoD personnel have a significant incentive to avoid giving candid responses to routine drug screening questions as the use of illicit substances (including marijuana or THC) violates the UCMJ and must be reported to the Service Member's command (see Substance Use Disorders in the Department of Veterans Affairs and the Department of Defense). If a Service Member with drug use disorder is command-directed to seek treatment, it may negatively impact their eligibility for assignments and career progression.

A recommendation statement by the USPSTF (2020) suggests asking questions about unhealthy drug use in adults aged 18 years or older.[e] This statement is rated a "B" and states that screening should only be implemented when services for accurate diagnosis, effective treatment, and appropriate care can be offered or referred. The evidence review from the USPSTF found that the identification of a drug use disorder by primary care screening followed by BI does not significantly impact the 3- or 12-month consumption outcome. Moreover, reductions in drug use disorder consumption outcomes were primarily based on those patients who were treatment-seeking as opposed to identified as having a drug use disorder by screening questionnaire.(119, 120) In contrast to the patient population studied by the USPSTF, there are potential harms associated with screening for drug use disorders in DoD (e.g., administrative, legal, and promotion-related). Therefore, the Work Group determined there is insufficient evidence to recommend for or against screening for drug use disorders in the primary care setting.

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed the evidence related to the recommendation.(118) The Work Group's confidence in the quality of the evidence was very low. The body of evidence was limited by being a single site observational study with very low confidence in the critical outcomes of enhanced assessment of drug use disorders and increased enrollment in drug use disorder treatment. The harms, including time, cost associated with the use of a screening tool, the stigma associated with identification of a drug use disorder, and lack of enhanced enrollment in therapy outweighed the benefits of increased identification of drug use disorders. Patient values and preferences varied somewhat. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Additional large-scale multicenter trials are needed to evaluate the benefits of screening for drug use disorders on increasing enrollment in drug use disorder treatment.

B. Treatment Setting

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.
   (Neither for nor against | Not reviewed, Amended)

Discussion

Identifying the appropriate level of care in SUD treatment is challenging, and a provider may consider numerous variables, including a patient's preferences, motivation, willingness, and the available resources.

[e] The USPSTF recommendation can be accessed here: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/drug-use-illicit-screening.

However, there is a lack of clear evidence to suggest that any specific factor accurately predicts the optimal level or intensity of care.

The American Society of Addiction Medicine Patient Placement Criteria (ASAM Criteria) have been widely promulgated to determine the level of care based on an 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).(121) However, controlled trials evaluating placement outcomes based on a standardized assessment of these dimensions are lacking. Nonetheless, the Work Group included this recommendation because some organizations now require a standardized assessment to determine the appropriate type of care.

As this is a *Not reviewed, Amended* recommendation, the Work Group did not review new evidence related to this recommendation. The Work Group's confidence in the quality of the evidence was not applicable because there is no known evidence supporting the use of these criteria. The Work Group considered the amount of time it takes to conduct long assessments, which results in the burdens outweighing the benefits. While the evidence supporting the use of standardized assessments is lacking, they can serve as thorough, multidimensional assessments for providers and patients willing to use them. Patient values and preferences are similar because of the length of time it takes to administer standardized assessments and complete other required items. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Future research is needed to evaluate whether recently developed software to conduct ASAM multidimensional assessments and yield an algorithmically derived placement recommendation based on the ASAM assessment dimensions and placement principles leads to better outcomes than clinical judgment alone.

C. Stabilization and Withdrawal

a. Alcohol Use Disorder

Recommendation

5. For the treatment of moderate-severe alcohol withdrawal, we recommend using benzodiazepines with adequate monitoring.
   (Strong for | Not reviewed, Amended)

Discussion

Moderate quality evidence from a meta-analysis by Amato et al. (2011) supports the use of benzodiazepines over placebo (risk ratio [RR]: 0.16; 95% CI: 0.04 to 0.69) for reducing seizure for moderate-severe alcohol withdrawal.(122) Compared to placebo, benzodiazepines reduce withdrawal severity, incidences of delirium, and withdrawal seizures. Benzodiazepines are generally well tolerated, although some sedation can occur. Adequate monitoring during alcohol withdrawal is required.

The potential for serious, potentially lethal outcomes that may occur during alcohol withdrawal, including seizure, further reinforces this recommendation and the need for appropriate supportive care, including monitoring vital signs and replacing fluids and electrolytes, which may require inpatient care during

moderate-severe alcohol withdrawal. Benzodiazepines that are ideal for the treatment of withdrawal include those with a rapid onset and long duration of action.(123) When considering treatment for patients who are pregnant, women should always be treated for acute withdrawal, including the use of supervised benzodiazepines when indicated, due to the risk of acute stress to the fetus and potentially dangerous alcohol withdrawal for the mother.

Providers hesitating to offer outpatient withdrawal management due to benzodiazepine-related safety concerns should consider options in Recommendation 6. Service Members who have not had problems of indiscipline (e.g., missed duty and DUIs) and are seeking care under the Army's Voluntary Care policy should not have their trust violated by a Medical Treatment Facility providing only inpatient alcohol withdrawal management, if they prefer to keep their care private from their chain of command. Inpatient withdrawal management entails missed duty and command notification and is not the least restrictive alternative when there is no history of alcohol seizures, delirium tremens, or other compelling clinical need.

Regarding adequate monitoring, severe alcohol withdrawal can be a life-threatening condition.(124-126) Some of the more dangerous manifestations of severe alcohol withdrawal are alcohol withdrawal delirium and withdrawal seizures that can progress to status epilepticus. Approximately 1 – 4% of hospitalized patients who have withdrawal delirium die.(125) Some of the more robust predictors of alcohol withdrawal delirium are prior episodes of delirium or withdrawal seizures.(124-126)

There has not been an RCT to test whether individuals with AUD who have a history of alcohol withdrawal delirium or seizures, and who are trying to stop alcohol use, would fare as well in outpatient management as they would with inpatient management. Such a study would not be approved by an institutional review board as it would be unethical to randomize patients who have a risk of death to a research control condition in which they might not be carefully monitored around the clock. Thus, determinations about adequate monitoring and the setting in which to perform such monitoring must be a clinical decision due to lack of evidence supported by GRADE type evidence. Most experienced providers would elect to manage a patient with a history of delirium tremens or withdrawal seizures undergoing a new episode of alcohol withdrawal in an inpatient setting with continuous monitoring.

There are relatively few harms associated with inpatient withdrawal management compared to outpatient management. There may be a higher likelihood of nosocomial infection in an inpatient setting, and the cost burden associated with inpatient care.

Patients with AUD and a history of alcohol withdrawal often have differing opinions regarding whether to go through medically supervised withdrawal in an inpatient versus outpatient setting. Many patients welcome the opportunity to be in a controlled environment where they have no access to alcohol and can be closely monitored and treated as indicated. Other patients do not wish to be hospitalized. For patients not at high risk of life-threatening complications of alcohol withdrawal, medically supervised withdrawal in the outpatient setting is reasonable; for Service Members seeking voluntary care, it may be highly preferable. For patients who are at high risk of life-threatening complications, many providers would not feel comfortable managing this type of alcohol withdrawal in the outpatient setting. Inpatient management requires far more expenditures of resources than does outpatient management.

As this is a *Not reviewed, Amended* recommendation, the Work Group considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(122) The confidence in the quality of the evidence was moderate. The benefits (e.g., decreased negative effects of alcohol withdrawal including seizures) outweighed the potential harms. There is little variation in patient values and preferences, as most patients want support in managing withdrawal symptoms. Given the moderate evidence from the 2015 VA/DoD SUD CPG in addition to the risk for very serious outcomes without withdrawal management, the Work Group decided upon a *Strong for* recommendation.

Recommendation

6. For managing mild-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 | Not reviewed, Not changed)**

Discussion

While the standard of care of treatment for alcohol withdrawal is benzodiazepines, sometimes there are risks associated with this treatment. For instance, patients may have inadequate monitoring available (e.g., inability to attend daily visits, lack of monitored settings), misuse liability (e.g., patient has history of misuse of sedatives), or documented allergy/adverse reaction to benzodiazepines. Thus, when the risks of benzodiazepines outweigh the benefits, the anticonvulsants gabapentin, carbamazepine, and valproic acid appear to be reasonable alternative agents for the management of alcohol withdrawal.(122, 127-129) In addition, because the use of benzodiazepines can be potentially harmful, and there are concerns of addiction and misuse, there is some concern about the use of benzodiazepines, particularly in mild alcohol withdrawal syndrome.

Although many studies to date examining non-benzodiazepine medications have been small, single-site randomized trials, the available evidence suggests that reduction of withdrawal symptoms, time to withdrawal completion, and adverse events are generally equivalent to benzodiazepines.(130, 131) However, more research is needed in this area. For instance, an SR by Liu et al. (2019) examined the use of baclofen for the treatment of alcohol withdrawal syndrome and found no conclusions could be drawn about the efficacy and safety of baclofen for the management of alcohol withdrawal syndrome.(132) In addition, a meta-analysis by Ahmed et al. (2019) examined the effectiveness of gabapentin in reducing cravings and alcohol withdrawal syndrome symptoms and found the use of gabapentin is at least moderately effective.(133) However, this conclusion was tempered by the limited number and rigor of existing studies. Direct comparisons with the existing standard of care (i.e., use of benzodiazepines) indicate that it is not entirely clear if these medications are equivalent to benzodiazepines for preventing withdrawal delirium or withdrawal seizures where there is elevated risk.

Although not reviewed by the Work Group, a recent SR and meta-analysis of the course of treatment using the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar) found that non-benzodiazipine medications for alcohol withdrawal have similar effectiveness compared to benzodiazepine therapy based on CIWA-Ar scores.(134) Thus, non-benzodiazepine medications may have particular utility for ambulatory medically supervised withdrawal when concerns exist about the prescribing of a controlled substance such as a benzodiazepine, although further research in this area is needed. While there is evidence of some

medications used as adjunctive medications for the treatment of alcohol withdrawal syndrome in addition to benzodiazepines (e.g., valproic acid, phenobarbital, dexmedetomidine), these studies were relatively small, tried only in intensive care settings, may not be appropriate for mild-moderate alcohol withdrawal syndrome and were not reviewed by the Work Group.(131, 135, 136)

The benefits of other, non-benzodiazepine medications likely outweigh the harms associated with no medications since alcohol withdrawal can be deadly. Moreover, patients likely would prefer medication treatment compared to no medication treatment.

As this is a *Not reviewed, Not changed* recommendation, the Work Group considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(122) The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations including a lack of direct comparisons of other non-benzodiazepine medications to benzodiazepines. Nevertheless, the risks of alcohol withdrawal syndrome are significant and, despite the lack of good evidence of effectiveness and relative mild risks when benzodiazepines are not available, other medications may be appropriate for the treatment of alcohol withdrawal syndrome. Thus, the Work Group decided upon a *Weak for* recommendation.

b. Opioid Use Disorder

Recommendation

7. For patients with opioid use disorder, we recommend against withdrawal management, without planned ongoing pharmacotherapy treatment, due to high risk of relapse and overdose (see Recommendations 16, 17, and 18).
   (Strong against | Not reviewed, Amended)

Discussion

For the treatment of OUD, patients who are provided medically supervised withdrawal, particularly those who do not receive formal, structured non-pharmacotherapy treatment, have high risk of relapse with resultant morbidity and mortality.(137, 138) Furthermore, evidence suggests opioid agonist treatment (OAT) is more effective than other pharmacotherapies over time and improves safety.(139, 140) Long-term methadone treatment has decades of demonstrated effectiveness. Studies have also shown buprenorphine to be used successfully in office-based settings over increasingly longer periods.(141-144) Additionally, patients utilizing buprenorphine to assist with opioid discontinuation demonstrate positive patient outcomes when used for longer-term treatment versus a quick taper.(145)

Notably, there are situations where medically supervised withdrawal from opioids may be preferred over long-term opioid agonist therapy. Examples include a taper of opioids using methadone, buprenorphine, or other symptom-treatment medications if patients (1) are entering an environment that requires abstinence from any opioids (e.g., prison, court-ordered abstinence-based treatment programs), (2) wish to receive non-opioid agonist treatment (e.g., treatment with injectable naltrexone), and (3) are in a profession that prohibits opioid agonist treatments (e.g., military, healthcare provider, air traffic controller). Buprenorphine can provide relatively short, safe, medically supervised withdrawal treatment.(146-151) 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.(152, 153) 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 testing (UDT).(154)

Despite general consistency in the evidence against withdrawal management alone for patients with OUD, there is some variability in patient preferences. While most patients would likely want to be treated with evidence-based medications, some patients do not want to be on OAT. Further, there is limited access to this treatment as methadone can only be dispensed through a limited number of highly regulated Opioid Treatment Program (OTPs), and buprenorphine can only be prescribed by providers who have been adequately trained and have attained the requisite U.S. Drug Enforcement Administration (DEA) waiver. Another consideration was the VA/DoD and national priority for providing evidence-based OUD medications to decrease suicide, overdose, and all-cause mortality.

As this is a *Not reviewed, Amended* recommendation, the Work Group considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(145, 154) The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including some studies with small sample sizes and imprecision. The major consideration regarding this recommendation is the high risk for catastrophic harms (e.g., overdose, suicide, all-cause mortality) in OUD patients treated with withdrawal management alone. Per GRADE guidelines: 15, which states, "A strong recommendation may be warranted . . . when low quality evidence suggests benefit in a life-threatening situation," the Work Group decided a *Strong* recommendation is warranted.(87) Patient values and preferences somewhat varied. Thus, the Work Group decided upon a *Strong against* recommendation.

Recommendation

8. For patients with opioid use disorder for whom opioid withdrawal management is indicated, we suggest using:
   - Buprenorphine/naloxone (in any setting); or
   - Methadone or buprenorphine/naloxone (in inpatient or accredited Opioid Treatment Programs) (see Recommendation 17).

   (Weak for | Reviewed, New-replaced)

Discussion

Opioid withdrawal management is only indicated under certain circumstances (e.g., for patients with OUD who will be treated with XR naltrexone or because a patient chooses not to be treated with opioid agonists). If medically supervised opioid withdrawal is indicated, the preferred approach is initial stabilization with methadone or buprenorphine followed by a short or extended taper. Buprenorphine and methadone maintenance are recommended for the treatment of OUD based on multiple RCTs and meta-analyses and the risks and benefits of OAT.(155-170)

Treatment completion is one metric of success, which some RCTs have evaluated. One study concluded that there are no significant differences in treatment completion with methadone versus buprenorphine; however, one study found methadone was superior to placebo.(137) Three RCTs concluded buprenorphine may be more effective than methadone.(149) In addition, buprenorphine and methadone were more effective than clonidine.(149) Rapid induction onto naltrexone ER using low dose naltrexone may be an option when OAT is not available or desired. One RCT demonstrated an 8-day induction onto

naltrexone ER versus the typical 15-day buprenorphine detoxification.(171) Finally, one study suggested no significant difference between methadone over clonidine in terms of treatment completion.(137) We found no evidence to support the addition of clonidine to a regimen of buprenorphine or methadone.

Despite general consistency in the evidence supporting the use of methadone or buprenorphine for opioid withdrawal management, patient preferences play an important role in medication selection. The stigma of 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.(137, 172)

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation and considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(156, 157, 159-170) The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including high attrition rates and imprecision. The benefit of improving symptoms of opioid withdrawal outweighed the potential harms, which were minimal. Patient values and preferences varied somewhat. Treatment with methadone, except for inpatient settings, might also be limited because OTPs are not available at many sites. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

9. For patients with opioid use disorder for whom withdrawal management is indicated and for whom methadone and buprenorphine are contraindicated, unacceptable, or unavailable, we suggest offering clonidine or lofexidine as a second-line agent for opioid withdrawal management (see Recommendation 17).
   (Weak for | Reviewed, New-replaced)

Discussion

Clinical situations may arise where the preferred pharmacotherapy (buprenorphine and methadone) for opioid withdrawal management is contraindicated, unacceptable, or unavailable. This may include patient preferences for declining treatment with opioid agonists. Readers are encouraged to review Recommendations 16 – 19 for medication treatment for opioid use disorder (MOUD) with buprenorphine, methadone, and naltrexone.

The Work Group reviewed two SRs and three RCTs of pharmacotherapy for withdrawal management. The Work Group evaluated outcomes of withdrawal symptoms and retention in treatment. An SR by Gowing et al. (2016) included 26 RCTs, though some did not meet this CPG's inclusion criteria.(173) The interventions included alpha2-adrenergic agonists versus placebo, methadone, or another alpha2-adrenergic agonist. The quality of the evidence was fair. Another SR, Gowing et al. (2017), included 27 RCTs.(174) The interventions included buprenorphine compared to clonidine, lofexidine, methadone, or to different rates of reduction of buprenorphine. The quality of the evidence was rated fair.

An RCT by Fishman et al. (2019) evaluated lofexidine versus placebo.(175) The quality of the evidence was fair for retention outcomes and poor for all other outcomes. Gorodetzky et al. (2017) examined lofexidine versus placebo.(176) The quality of the evidence was fair for retention outcomes and poor for all other outcomes. Dunn et al. (2017) studied tramadol extended-release versus clonidine versus buprenorphine with a poor quality rating.(177)

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation (173-177) and considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG. The Work Group's confidence in the quality of the evidence was low. The benefits of improved withdrawal symptoms outweighed potential harms (minimal side effects and adverse events [hypotension for lofexidine and clonidine]), and patient values and preferences varied somewhat. Thus, the Work Group decided upon a *Weak for* recommendation.

c. Sedative Hypnotic Use Disorder

Recommendation

10. For patients in need of withdrawal management for benzodiazepines, we recommend gradually tapering benzodiazepines.
    (Strong for | Reviewed, New-replaced)

Discussion

Benzodiazepine discontinuation is associated with three characteristic symptoms: recurrence, rebound, and withdrawal. Optimal clinical management of benzodiazepine discontinuation, including avoidance of abrupt drug discontinuation, can lessen withdrawal symptoms and promote successful drug discontinuation or dose reduction.(178) Seizures can occur with abrupt discontinuation, and other symptoms can include paranoid thoughts, hallucinations, and delirium.

The recommended clinical approach to benzodiazepine discontinuation is gradual dose tapering with consideration of patient symptoms and tolerability. Few data exist on the optimal rate of tapering; optimal duration of withdrawal may vary by patient. The early stages of withdrawal are easier to tolerate than later stages so tapering schemes usually start with an early rapid step-down in dose followed by a slower rate of reduction.(178) Low dose use of benzodiazepines can be tapered by 20% per week; however, higher dose benzodiazepine withdrawal should be conducted over an 8 – 12 week period, and up to six months or longer may be necessary in exceptional cases.(178) A commonly used slow tapering strategy in a higher dose patient is weekly 25% dose reduction until 50% of the dose remains, followed by a one-eighth dose reduction every four to seven days.(179) Slow tapering schedules are associated with total cessation of benzodiazepine use in about two-thirds of patients.(178)

Benzodiazepines with a shorter half-life may precipitate withdrawal sooner than a longer-acting benzodiazepine. Switching from a short-acting benzodiazepine to a longer-acting benzodiazepine may not improve outcomes, although it may be advantageous to convert multiple benzodiazepines to one. Providers may consider switching to a longer-acting benzodiazepine, such as diazepam, depending on patient and provider preference. Additionally, differences in metabolism and pharmacokinetic profiles should be considered in older adults when determining an agent for tapering. 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.

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).(180, 181) Patients should be monitored throughout the tapering period for withdrawal symptoms and for the disorder being

treated; emergence of severe withdrawal symptoms signals a need to slow the tapering process. Some patients may prefer an inpatient taper and withdrawal schedule, but due to resources and the long, slow tapering process, an outpatient taper in a primary care setting is often the most feasible.

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation and considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG. The Work Group's confidence in the quality of the evidence was very low because the studies were small. Patient values and preferences were similar, as most patients would want to receive this treatment. Years of clinical experience and the potentially life-threatening nature of these conditions warrant a *Strong for* recommendation, as the benefits of gradually tapering patients off benzodiazepines outweighed the harms of a potentially fatal withdrawal. Additionally, due to the significant risk of seizures associated with abrupt discontinuation, the risks of abrupt cessation far outweigh the benefits. Per GRADE guidelines: 15, which states, "A strong recommendation may be warranted . . . when low quality evidence suggests benefit in a life-threatening situation," the Work Group decided upon a *Strong for* recommendation.(87)

Recommendation

11. There is insufficient evidence to recommend the use of adjunctive medications for the treatment of benzodiazepine withdrawal.
    (Neither for nor against | Reviewed, New-added)

Discussion

The Work Group reviewed the literature for adjunctive medications for the treatment of benzodiazepine withdrawal (see Recommendation 10 for further information on benzodiazepine withdrawal management). An SR by Baandrup et al. (2018) is the only study that met this CPG's inclusion criteria.(182) The interventions included alpidem, buspirone, captodiame, carbamazepine, flumazenil, paroxetine, pregabalin (PGB), propranolol, tricyclic antidepressants (TCAs), and valproate. The critical outcomes reviewed included benzodiazepine discontinuation, withdrawal symptoms, and relapse. The studies were rated very low quality, resulting in a very low confidence in the quality of evidence.

Baandrup et al. (2018) found mixed results, which suggests the current state of the evidence does not support the use of additional pharmacotherapies in patients undergoing benzodiazepine taper to reduce or discontinue benzodiazepine use.(182) While there was a slight improvement in withdrawal symptoms with captodiame, flumazenil, paroxetine, pregabalin, and TCAs, significant harms were also noted. These harms included rapid precipitated withdrawal with flumazenil and worsening rates of benzodiazepine use with alpidem. The literature base is limited by very small sample size and study quality, and paucity of data for most interventions.(182)

The Work Group noted a large variation in patient values and preferences, dependent upon comorbidities and medication tolerability concerns. Although very weak evidence exists, it is insufficient to warrant a recommendation for or against the use of adjunctive medications for the treatment of benzodiazepine withdrawal.

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation.(182) The confidence in the quality of evidence was very low.

Harms/burdens (e.g., rapid precipitated withdrawal with flumazenil and worsening rates of benzodiazepine use with alpidem) slightly outweighed the benefits. Patient values and preferences largely varied. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

D. Treatment

a. Alcohol Use Disorder – Pharmacotherapy

Recommendation

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

    (Strong for | Not reviewed, Amended)

Discussion

Two RCTs (183, 184) and three SRs/meta-analyses (185-187) showed moderate quality evidence that naltrexone and topiramate improved alcohol consumption outcomes for the treatment of AUD. These clinical trials were based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (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 after 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 medications over another; therefore, treatment should be individualized considering patient preferences and history. These medications are presented below in alphabetical order. Additional information can be found in Appendix B.

Naltrexone

A multi-center RCT by Anton et al. (2006) (Combining Medications and Behavioral Interventions [COMBINE]) and an SR and meta-analysis by Jonas et al. (2014) found naltrexone improves alcohol consumption outcomes (e.g., percent heavy drinking days, number of drinks per day, return to heavy drinking, and percent drinking days) in patients with AUD.(184, 187) 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 clinical outcomes.(187) However, injectable naltrexone should be considered when medication adherence is a significant concern and the patient is agreeable to receive monthly injections by a provider. Naltrexone injection must be stored under refrigeration, so distribution to Service Members deployed to remote locations may be problematic. In a 9-arm trial, Anton et al. (2006) compared oral naltrexone and/or acamprosate to double placebo on a platform of addiction-focused medical management with or without a combined behavioral intervention (CBI).(184) They found that patients

receiving addiction-focused medical management with naltrexone, CBI, or both fared better on drinking outcomes than those receiving acamprosate or double placebo.

Topiramate

A meta-analysis by Blodgett et al. (2014) found topiramate improved combined abstinence and heavy drinking outcomes and may decrease alcohol reinforcement and the propensity to drink by reducing craving for alcohol through antagonism of glutamate receptors and inhibition of dopamine release.(185) While topiramate is not approved for AUD by the U.S. Food and Drug Administration (FDA), it is recommended because of the moderate quality evidence for a significant reduction in heavy drinking and promotion of abstinence.(185, 187) Moreover, a pilot RCT by Batki et al. (2014) in Veterans with AUD and co-occurring PTSD showed benefit associated with topiramate in reducing alcohol consumption, craving, and PTSD symptom severity.(183)

Summary

There is some variability in patient preferences regarding these medications. Side effects associated with naltrexone, including initial transient nausea, tend to be minimal, and there are options for monthly injection or once-daily dosing. In contrast, topiramate may cause dizziness, negative cognitive effects, or weight loss. Oral naltrexone and topiramate are both available as low cost generics, whereas injectable naltrexone has a higher associated cost and some feasibility concerns (e.g., difficult to administer outside of a clinic with nursing support and requires on-site refrigeration or timely transport by patients from their pharmacy). Topiramate may require multiple visits for adequate titration and tolerability assessment.

As this is a *Not reviewed, Amended* recommendation, the Work Group considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(183, 185, 187) The Work Group's confidence in the quality of the evidence was moderate. The benefits of naltrexone (e.g., reducing alcohol consumption and craving) outweighed the potential adverse effects. The benefits of topiramate for alcohol consumption outcomes outweighed potential harms, but a variety of adverse effects that ranged in severity and possible challenges with dose titration occurred. Patient values and preferences somewhat vary given the tolerability concerns for both medications. Also, naltrexone's opioid blockade effect may preclude use in patients who require opioid pain medications. Despite these minor concerns, given the overwhelming body of positive evidence for efficacy of these medications, the Work Group decided upon a *Strong for* recommendation.

Recommendation

13. For patients with moderate-severe alcohol use disorder, we suggest offering one of the following medications:
    - Acamprosate
    - Disulfiram

    (Weak for | Not reviewed, Amended)

Discussion

Several SRs/meta-analyses with low quality evidence for alcohol consumption outcomes support the use of acamprosate and disulfiram for the treatment of AUD.(186-188) These trials used DSM-IV criteria for alcohol dependence, which is equivalent to DSM-5 criteria for moderate-severe AUD. Either of these

medications should be offered in conjunction with a psychosocial intervention and following the preferences of appropriately informed patients.

There is insufficient evidence to recommend for or against the routine use of one of these suggested medications over another, except in the presence of contraindications; therefore, treatment should be individualized considering patient preferences, tolerability, and prior treatment history. These medications are presented below in alphabetical order. Additional information can be found in Appendix B.

Acamprosate

Meta-analyses by Donoghue et al. (2015) and Jonas et al. (2014) found acamprosate improved alcohol consumption outcomes relative to placebo, most notably return to drinking after abstinence.(186, 187) Acamprosate may act by normalizing central glutamatergic dysregulation in AUD, thereby relieving symptoms of prolonged alcohol withdrawal.(186) Numerous European trials found acamprosate effective in improving consumption outcomes, whereas some U.S. trials have failed to show such benefits.(186) European studies of acamprosate have shown a significantly reduced risk of discontinuing treatment for any reason, whereas trials conducted in the rest of the world have demonstrated an increased risk of treatment discontinuation associated with acamprosate.(186) These discordant results may have been due to methodological differences between the 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.(186)

The divided dose administration three times daily and large tablet size presents a challenge to many patients and can negatively affect treatment adherence. Acamprosate may be considered for patients with AUD who are also taking prescribed opioids or who have significant hepatic damage/impairment since it is not subject to hepatic clearance. Patients who are highly motivated, abstinent before initiation, and not discouraged by the burden of three times-daily dosing are well suited for acamprosate. Based on patient values and preferences, some patients and providers may choose other agents that are dosed once daily.

Moderate quality evidence of significantly elevated rates of certain adverse events (e.g., anxiety, diarrhea, and vomiting) suggests there is some level of harm associated with acamprosate. However, this moderate quality evidence supported findings of significantly reduced return to any drinking and drinking days associated with acamprosate, at least in the outpatient specialty care setting, with very low to low quality evidence demonstrating no significant between-group differences in return to heavy drinking and heavy drinking days.(187)

Disulfiram

Disulfiram is a medication used to support a behavioral paradigm in which a pharmacologically-induced aversive experience overcomes the human tendency to discount delayed larger punishments in favor of immediate smaller rewards. The disulfiram-alcohol reaction overrides the immediate smaller reward of alcohol intoxication with a timely adverse reaction. It is the expectation of this alcohol-disulfiram reaction that mediates disulfiram's efficacy by altering the patient's decisional balance in favor of abstinence.

A meta-analysis of 22 RCTs by Skinner et al. (2014) showed statistically significant efficacy of disulfiram for AUD compared to a variety of control conditions.(188) The authors hypothesized that double-blind, placebo-controlled trials of disulfiram would mask its efficacy by distributing the expectation of the

alcohol-disulfiram reaction evenly across patient groups. In comparing blind versus open-label RCTs, only open-label trials significantly favored disulfiram over the control conditions. Among open-label trials, those in which disulfiram administration was monitored (e.g., by a spouse or by the clinic) showed the largest effect size favoring disulfiram.(188)

Patients taking disulfiram should avoid ingestion of alcohol due to the expectation of a toxic reaction if alcohol is consumed; thus, the optimal assessment of disulfiram efficacy may have resulted from open-label trials where patient awareness of active treatment allowed the treatment to have its full preventive effect.(188) The human tendency to avoid punishment may inhibit adherence to disulfiram, thus reducing its effectiveness when administration is unsupervised by a clinician or family member. Skinner et al. (2014) showed no advantage of 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.(188) Some RCTs directly comparing disulfiram to naltrexone, acamprosate, and topiramate also favored disulfiram.(188)

Because the action of disulfiram depends on the expectation of adverse effects, it should not be given to patients who are unable to consider the consequences of alcohol consumption while taking disulfiram. Disulfiram is thus best suited for 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 when disulfiram is combined with alcohol, the risks and benefits of disulfiram should be carefully considered.

Low quality evidence suggests there are potential harms associated with disulfiram, including increased risk of adverse events among patients receiving disulfiram.(188) Disulfiram should only be used when abstinence is the goal, established with patient concurrence, and when initiated with addiction-focused counseling. Enlisting clinic personnel or a supportive significant other to observe daily disulfiram doses will optimize disulfiram treatment outcomes. Providers should document verification of alcohol abstinence and the informed consent discussion with patients before initiating disulfiram.

Summary

Despite general consistency in the evidence supporting acamprosate and disulfiram, acamprosate tended to perform better in studies conducted outside of the U.S. than in the U.S. There is some variability in patient preferences regarding acamprosate, with benefits outweighing possible harms. Side effects associated with acamprosate tend to be minimal aside from initial diarrhea or nausea, but patients may be deterred by thrice-daily dosing.

The benefits of disulfiram may only slightly outweigh potential harms because of its associated toxicity when combined with alcohol and potential side effects that pose tolerability concerns. There are rare but serious adverse effects associated with disulfiram, including hepatitis or fulminant liver failure. Thus, indices of liver health must be monitored regularly during the first several months of disulfiram treatment.

Disulfiram and acamprosate are both available as low-cost generics. Acamprosate may be preferable in individuals with hepatic disease. Disulfiram may be most appropriate for highly motivated patients seeking sobriety who may be strongly motivated to curtail alcohol use or who are willing to have disulfiram dosing observed by a significant other.

As this is a *Not reviewed, Amended* recommendation, the Work Group considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(187, 188) The Work Group's confidence in the quality of the evidence regarding both medications was low. The body of evidence for alcohol consumption outcomes associated with acamprosate had serious limitations in study quality. There was low quality evidence for all reported disulfiram outcomes as a result of very serious limitations for overall abstinence outcomes and serious limitations for other consumption outcomes (i.e., return to drinking, percent drinking days). The benefits for alcohol consumption outcomes outweighed potential harms for acamprosate (e.g., diarrhea, nausea) and slightly outweighed potential harms for disulfiram (e.g., toxicity when combined with alcohol, adverse effects, hepatic toxicity). Patient values and preferences varied somewhat given tolerability concerns and acamprosate's frequent dosing regimen. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

14. For patients with moderate-severe alcohol use disorder for whom first-line pharmacotherapy is contraindicated or ineffective, we suggest offering gabapentin.
    (Weak for | Not reviewed, Not changed)

Discussion

In an RCT (n=150) by Mason et al. (2014), gabapentin in combination with counseling significantly improved rates of abstinence and heavy drinking in individuals with DSM-IV alcohol dependence; however, the single-site setting and high dropout rate raised concerns regarding its potential for bias and limited generalizability.(189) An RCT by Anton et al. (2011) demonstrated the addition of gabapentin to oral naltrexone improved drinking outcomes relative to naltrexone alone in the first six weeks after drinking cessation.(190)

Although not included in this CPG's evidence review, and therefore not used in determining the strength of this recommendation, a recent multisite RCT of extended-release gabapentin for AUD treatment did not demonstrate significant differences in alcohol use or cravings between the active medication and placebo groups.(191) However, a single-site RCT by Anton et al. (2020) showed reduced alcohol consumption in participants with higher pre-study withdrawal symptom severity, suggesting that gabapentin may be more effective in individuals with alcohol withdrawal symptoms.(192)

The effects of gabapentin likely occur through modulation of γ-aminobutyric acid (GABA) activity in the amygdala associated with AUD. The need for more frequent dosing than once daily may make adherence difficult for some patients. There are increased concerns regarding the misuse potential of gabapentin, with reports of patients (e.g., individuals with opioid misuse or other SUDs) taking doses higher than prescribed for euphoric effects.(193) When taken as directed, however, gabapentin has a high margin of safety, and many primary care providers who prescribe it for non-AUD indications may be more comfortable prescribing it than some of the first line treatments. Gabapentin may be an option for patients with AUD and co-occurring neuropathic pain, or for some with sleep disorders. Also, since gabapentin is eliminated renally, it may be an option for patients with clinically significant hepatic disease.

The Work Group noted that the relative benefits in alcohol consumption outcomes and use for the treatment of pain conditions slightly outweighed the harms, which include some potential for misuse and

central nervous system (CNS) depressant effects. There is some variation in patient preferences for gabapentin due to tolerability. There is broad access to gabapentin due to its low cost and wide acceptability in primary care settings.

As this is a *Not reviewed, Not changed* recommendation, the Work Group considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(187, 189) The Work Group's confidence in the quality of the evidence was low. The benefits (e.g., reduced alcohol consumption) slightly outweighed the potential harms (e.g., potential for misuse and CNS depressant effects). There is some variation in patient values and preferences. Thus, the Work Group decided upon a *Weak for* recommendation.

More research is needed on the safety and effectiveness of gabapentin and other medications treatments for AUD.

b. Alcohol Use Disorder – Psychosocial Interventions

Recommendation

15. For patients with alcohol use disorder, we suggest one or more of the following interventions, considering patient preference and availability:
    - Behavioral couples therapy
    - Cognitive behavioral therapy
    - Community reinforcement approach
    - Motivational enhancement therapy
    - 12-step facilitation

    (Weak for | Not reviewed, Amended)

Discussion

A brief description of these psychosocial interventions and evidence for their use for patients with AUD is below in Appendix C.

Most versions of behavioral couples therapy (BCT) focus on reducing alcohol use in the patient and improving overall marital/relational 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 for AUD teaches patients to modify thinking and behavior related to alcohol use. Moreover, it focuses on changing 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 strengthen coping skills, improve mood and interpersonal functioning, and enhance social support. Treatment incorporates structured practice outside of sessions, 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 influence the patient's behavior. Since 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/her drinking behaviors so that a sober lifestyle is more rewarding than one dominated by alcohol. Community reinforcement approach 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 (e.g., attending treatment, taking medication, or being abstinent).

Motivational enhancement therapy (MET) is a less intensive psychosocial intervention for patients with AUD. It uses principles of MI to heighten awareness of ambivalence about change, promote commitment to change, and enhance self-efficacy. Motivational enhancement therapy differs from MI in that it is a more structured intervention 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 the 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 AA or other 12-step-based group mutual help resources. This approach is systematized in a manual and delivered as 12 sessions of individual therapy in which the therapist actively encourages engagement in AA and explains the AA program's first four steps. 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 the development of a plan for recovery-oriented activities (e.g., meeting attendance, sponsor contact). Other interventions based on TSF have also focused on increasing positive social support outside of 12-step programs.

Based on the 2015 VA/DoD SUD CPG evidence review, these psychosocial interventions (i.e., BCT, CBT, CRA, MET, and TSF) may modestly improve some outcomes of consumption, adherence, and recovery in patients with AUD. The current systematic evidence review did not impact this recommendation, as the new studies identified were comprised of lower quality evidence, smaller sample sizes, or were indirect.

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.(194-197) Behavioral couples therapy generally has positive effects on marital satisfaction as well.

Three SRs indicated CBT is generally more effective than minimal or control comparators for individuals with AUD, but not superior to other active treatments.(198-200) Other individual studies of CBT in patients with AUD and mental health comorbidities generated mixed results, with one study finding positive effects (201) and two others finding positive effects at some follow-up points.(202, 203)

The combination of CBT plus MI appears to be more effective than comparison conditions for individuals with AUD and co-occurring anxiety or depressive disorders.(204)

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.(205, 206)

12-step facilitation and other treatments designed to increase participation in self/mutual help programs and other sources of social support in the community have consistently increased participation in these programs and produced greater improvements in some drinking outcomes compared to CBT or MET, including measures of abstinence.(205)

The confidence in the quality of the evidence was low, with benefits outweighing harms. The 2015 VA/DoD SUD CPG included moderate and low quality studies, but the current Work Group's analysis found the overall study quality rating to be low. Because of the large variation in patient values and preferences for psychosocial interventions, we suggest offering a menu of options using a shared decision making approach based on provider skills and patient preferences. This may increase the likelihood of participation in the therapeutic modality. None of the different interventions were better than any of the others, but there is a suggested benefit with any psychosocial intervention over no psychosocial intervention.

These interventions require considerable training to implement with fidelity, and delivery can be resource-intensive. The evidence is based almost entirely on studies in which these interventions were delivered individually to patients, whereas most psychosocial interventions for AUD in the VA and DoD are delivered in groups. Moreover, these modes of treatment may not be available at all facilities. Finally, there is less known about the efficacy of some of these interventions within specific subgroups (e.g., cultural, ethnic, and/or gender minorities). There can be burdens due to lack of transportation or the time demands required for these treatments. Also, BCT requires the patient to have a partner able and willing to participate.

As this is a *Not reviewed, Amended* recommendation, the Work Group considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(194-196, 198-204) The Work Group's confidence in the quality of the evidence was low. The body of evidence had limitations including using different types of each intervention, limitations in descriptions of populations, prevalence of other behavioral health diagnoses or SUD medication treatment, length of time to outcome measures and different outcome objectives (i.e., decreased days of heavy drinking versus abstaining), and variable follow-up (13 weeks to 18 months). The potential benefits outweighed the minimal harms (i.e., burden of travel time, which could be considerable in some treatment locations, and duration of the intervention [up to 18 months]). Thus, the Work Group decided upon a *Weak for* recommendation.

c. Opioid Use Disorder – Pharmacotherapy

Recommendation

16. For patients with opioid use disorder, we recommend one of the following strategies:
    - Buprenorphine/naloxone in any setting; or
    - Methadone or buprenorphine/naloxone provided through an accredited Opioid Treatment Program

    (Strong for | Reviewed, Amended)

Discussion

Opioid Agonists in General

Formulations of buprenorphine and methadone, often referred to as OAT, are recommended for the treatment of OUD. This recommendation is based on multiple RCTs and meta-analyses with high quality

evidence for the outcomes treatment retention and illicit opioid abstinence, and moderate quality evidence for the outcome mortality. Moderate quality evidence supports the use of OAT over psychosocial treatment alone to improve outcomes for OUD.(145, 155-157, 207-218) In addition, the benefits strongly outweigh the risks given the risk of fatal outcomes if OUD remains untreated. If a patient refuses or defers OAT, we suggest using a motivational approach to encourage reconsideration. One motivational strategy is to provide various treatment options in various treatment settings (e.g., primary care, mental health, or OTP environments), as there may be variations in values and preferences among patients with OUD in the type of OAT and the setting where treatment occurs.

Opioid agonist treatment consists of administering or prescribing a medication, such as methadone or sublingual, buccal, or injectable buprenorphine. Comprehensive medical, counseling, and rehabilitative services may be offered as indicated based on patient need, willingness, and preference. By administering or prescribing an opioid to prevent withdrawal, reduce craving, and reduce the effects of illicit opioids, the patient with OUD can focus on recovery activities. In addition, OAT has been associated with a reduction in human immunodeficiency virus (HIV) infection risk, drug-related crime, and other outcomes. When compared to medically supervised withdrawal, longer-term 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.(145)

Four SRs showed that using OAT for the treatment of OUD was effective in both accredited OTPs and within general medical settings.(156, 207, 214, 215) Opioid Treatment Programs 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.(219) Opioid Treatment Programs can provide opioid maintenance and withdrawal management using methadone or buprenorphine.

Opioid Treatment Programs must have a SAMHSA certification and current accreditation. 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. In the U.S., methadone can be dispensed within OTPs only, whereas formulations of buprenorphine can also be prescribed by accredited clinicians in office-based settings such as primary care, outpatient specialty SUD treatment, pain clinics, and general mental health clinics. Thus, buprenorphine is more accessible to some patients. Buprenorphine treatment in office based settings can be individualized to patient needs and there are several clinical settings and models of care where it can be offered, in VA and other settings.(220)

Buprenorphine

Three RCTs demonstrate the effectiveness of buprenorphine treatment.(145, 208, 221) Most buprenorphine treatment studies reviewed included both the buccal and sublingual forms of buprenorphine and the combination-product buprenorphine/naloxone. Buprenorphine/naloxone is recommended in most situations because it discourages intravenous use and decreases risk of diversion. Other buprenorphine formulations such as the extended-release injectable buprenorphine have not been

as extensively studied, but trials have shown some improvement over placebo and comparative effectiveness to other buprenorphine formulations.(222, 223) However, there is insufficient evidence to recommend any one of the different FDA-approved formulations or routes of delivery of buprenorphine over another (see Recommendation 18).

Compared to highly-controlled methadone treatment in OTPs, treatment with buprenorphine can be provided outside of an OTP by practitioners who have received a waiver from SAMHSA and have a special U.S. Drug Enforcement Administration (DEA) number (X-waiver). Qualified practitioners include physicians, nurse practitioners, physician assistants, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse-midwives. Physicians can qualify for a waiver under the Drug Addiction Treatment Act of 2000 (DATA 2000) by completing an approved eight-hour training course or meeting other specific criteria. Non-physician qualified practitioners can qualify for a waiver by completing an approved 24-hour training course. Qualified practitioners can apply for a SAMHSA waiver to begin treating 30 patients and certain providers may immediately be able to treat up to 100 patients in qualified practice settings. After one year, qualifying practitioners who meet certain criteria can apply to SAMHSA to increase their treatment limit to 100 patients, and later 275 patients.(224) As of July 2021, there is some movement to modify the x-waiver process in the U.S.

Overall, the benefits of OAT significantly outweigh potential harms. Patient values and preferences may vary, particularly for active duty Service Members and those in safety-sensitive positions. Some patients may want office-based care using buprenorphine, some may want methadone or buprenorphine treatment in OTPs, and others may refuse agonist medication altogether.

Evidence also suggests buprenorphine is effective in various real-world settings for different patient populations, including those who are homeless or infected with HIV.(64, 141, 142, 225-227) Meta-analyses of studies comparing buprenorphine treatment to methadone treatment indicate that, overall, both are equivalent in terms of suppressing illicit opioid use, but methadone has slightly better treatment retention.(214)

Methadone and Methadone Maintenance Therapy

Decades of experience with methadone maintenance therapy (MMT) in OTPs have yielded significant evidence that methadone enhances treatment outcomes. Flexible dosage strategies are better than fixed dosage strategies for improving retention.(207) Under usual practices, a stable target dose is >60 milligrams (mg)/day, and many patients will require considerably higher doses to achieve a pharmacologic blockade of reinforcing effects of illicit opioids.

The 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 often fatal, but extremely rare. Two studies found no correlation between methadone daily dose and corrected QT interval (QTc) (the heart rate corrected time from the start of the Q wave to the end of the T wave).(228, 229) Other risk factors must be considered (e.g., history of heart disease and concurrent medications that also prolong QTc). The benefits of MMT also outweigh the harms for many secondary outcome measures. Evidence suggests methadone reduces the morbidity and criminality associated with heroin use, improves social engagement and vocational productivity, and prevents the spread of blood-borne diseases associated with sharing needles.(215)

Clinicians and patients have varying preferences regarding methadone treatment. Some providers are concerned about methadone's adverse effects including prolonging the QTc and significant drug interactions within the CYP450 system, and respiratory depression. Patients may not want to come to OTPs frequently to receive methadone, as it is less geographically available due to regulations that restrict methadone treatment to OTPs with strict guidelines for observed dosing, supervised treatment, and associated services. In addition, MMT has mission-readiness implications for active duty personnel and patients in safety-sensitive positions. Military personnel, for example, are not deployed if they are on MMT. Access to MMT is also limited by the availability of OTPs, which are not available at many facilities.

Active Duty Service Members and Opioid Agonist Treatment

It is important to note that the OAT studies underlying this recommendation have not been conducted in active duty settings. In the DoD setting where Service Members are regularly randomly tested for illicit or illegitimate drug use, and the long-term prescription of opioids is very closely monitored at both the patient and provider level, DoD practitioners rarely see OUD patients with the significant chronicity common in other settings. Additionally, within the DoD, Service Members are directed to be separated from service when they have a problem that renders them "non-deployable into harm's way" for more than 12 months. This 12-month policy restriction applies to OAT and limits the duration of possible treatment in most active duty cases since OAT would complicate the treatment of acute traumatic pain in battlefield conditions and since providers and commanders must be confident that a Service Member is deployment-ready (which requires a period of stability without OAT). In the context of less chronic illness and deployment/career limitations posed by OUD and OAT (and perhaps strong motivation to address OUD and salvage the military career) some DoD patients, in dialogue with their provider, may choose a trial of limiting any medication for treating their OUD to a brief period addressing only acute opioid withdrawal symptoms (see also Recommendation 9).

Pregnant Women with Opioid Use Disorder

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 fourfold in the past decade.(230) It was also reported that the incidence of neonatal opioid withdrawal syndrome (NOWS) (previously referred to as neonatal abstinence syndrome) identified at delivery increased almost threefold in the past decade.(230, 231)

Since the 1960s, methadone has been the most common medication to treat pregnant women with OUD and has been associated with positive maternal and neonatal outcomes.(232, 233) Since the advent of buprenorphine to treat OUD in 2002, there has been increased interest in using it to treat OUD in pregnancy, as access to methadone has not been robust for patients who are pregnant, mainly due to geographical or ideological considerations. Buprenorphine has been found to improve maternal and infant outcomes among pregnant patients with OUD, particularly incidence and severity of NOWS and opioid-use related outcomes. Based primarily on Jones et al. (2012), treatment with buprenorphine was associated with similar maternal and infant outcomes to treatment with methadone (the established standard of care for patients with OUD who are pregnant).(233)

It is important to note that the mono-product of buprenorphine (i.e., not buprenorphine/naloxone) was used in the previously cited clinical trial to minimize risks to the fetus. Two small pilot studies, cited in the

2015 VA/DoD SUD CPG, 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 (234) or compared to matched controls receiving methadone.(235) 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. Finally, an observational study that evaluated birth weight, preterm delivery, congenital anomalies, and stillbirth among infants born to patients who were pregnant with OUD and on the combination product found no harm from taking the combination product in pregnancy.(236) There is currently no evidence to suggest that buprenorphine/naloxone carries additional risk compared to buprenorphine alone in pregnancy.

Patient choice is an important factor in deciding between methadone and buprenorphine in pregnancy. However, providers should consider the availability of medication, as buprenorphine is more widely available in some settings than methadone.

Summary

As this is a *Reviewed, Amended* recommendation the Work Group systematically reviewed evidence related to this recommendation and considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(157, 214) The Work Group's confidence in the quality of the evidence was moderate, although high quality evidence existed for treatment retention and opioid consumption. Additionally, the Work Group chose a *Strong for* recommendation due to the balance of risks/benefits given the risk of fatality for untreated OUD. The body of evidence had some limitations including high attrition rates in some studies. The benefits (e.g., reduction in all-cause mortality, reducing craving, the effects of illicit opioids, HIV and hepatitis infections, drug-related crime, and opioid use and the associated consequences) significantly outweighed the harms/burdens (e.g., side effects of buprenorphine, including common side effects such as constipation, dizziness, drowsiness, headache and nausea, and rare side effects such as irregular heartbeat; side effects of methadone, including common ones such as constipation, dizziness, drowsiness, headache, and nausea, as well as respiratory depression [uncommon] and Torsades de pointes [rare]). In addition, when compared to medically supervised withdrawal attempts, OAT is better in achieving improved outcomes.(138) Patient values and preferences vary somewhat because some patients are concerned about the stigma attached to being on OAT. Also, OAT has mission-readiness implications for active duty personnel and patients in safety-sensitive positions. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

17. For patients with opioid use disorder, we suggest offering extended-release naltrexone (IM).
    (Weak for | Reviewed, New-replaced)

Discussion

Intramuscular (IM) extended-release (XR) naltrexone is an appropriate treatment for OUD, but clinicians should account for the requirement for 7 – 10 days of opioid abstinence before initiation.(237-240) An RCT by Sullivan et al. (2019) compared naltrexone XR to oral naltrexone, and results favored the former (IM) for treatment retention but did not achieve significance for opioid consumption.(237) An RCT by Krupitsky et

al. (2011) demonstrated that naltrexone XR (IM) reduced opioid consumption and improved retention for patients with OUD compared to placebo.(238)

Two other RCTs evaluated the comparative effectiveness of naltrexone XR (XR-NTX) with buprenorphine/naloxone (BUP-NX) for the treatment of OUD. Lee et al. (2018) randomized 570 patients to receive XR-NTX (n=283) or BUP-NX (n=287) in their large, multicenter, open-label trial.(239) The XR-NTX group struggled with induction with 72% (204/283) successful versus 94% (270/287) in the BUP-NX group. In this intent-to-treat (ITT) population, relapse events were greater in the XR-NTX 65% (185/283) versus 57% (163/287) in the BUP-NX which was statistically significant but attributed primarily to induction failures in the XR-NTX group.(239) For those who were successful in achieving induction (per-protocol population), both XR-NTX and BUP-NX appeared to be safe and effective treatment options with 24-week relapse rates, opioid-negative urine samples, and opioid abstinent days similar across study groups.(239) Tanum et al. (2017) compared XR-NTX vs BUP-NX in a 12-week, multicenter, open-label, non-inferiority trial that randomized 159 patients, who had all completed full withdrawal from opioids, with 79 in BUP-NX and 80 in XR-NTX groups respectively.(240) Naltrexone XR was non-inferior to BUP-NX in treatment retention and opioid negative urine drug tests. In the superiority analysis, XR-NTX had significantly lower use of heroin and other illicit opioids than BUP-NX.(240)

The benefits related to abstinence and treatment retention significantly outweigh harms for XR-NTX, and other than injection site reactions, there are very few significant adverse events. Patient values and preferences regarding the use of XR-NTX may have significant variation depending on access to treatment, eligibility for OAT, preference for oral versus injectable, and active military service.

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation (237, 239, 240) and considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(238) The confidence in the quality of the evidence was very low for the outcomes evaluated. The quality of evidence was poor with limitations including lack of blinding, moderate attrition, ITT results not reported (240), and induction protocol,(239) limiting interpretation and generalizability. Comparative effectiveness studies provided mixed results but demonstrate that XR-NTX's benefits outweighed potential harms. Patient values and preferences, particularly the willingness to go through opioid withdrawal before starting medication as is necessary with naltrexone, the acceptability of injectable therapy, and implications for active duty Service Members, may guide use. Cost and accessibility may also inform treatment choice. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

18. There is insufficient evidence to recommend any one of the different FDA-approved formulations or routes of delivery of buprenorphine over another.
    (Neither for nor against | Reviewed, New-added)

Discussion

New formulations of buprenorphine for OUD continue to emerge and feature various routes of delivery, in a crowded drug development pipeline with multiple FDA approvals since 2015. In the absence of more robust comparative effectiveness data, we encourage clinicians to cautiously consider the options and temper the proposed benefits of alternative formulations with their relative cost of care.

An RCT by Lofwall et al. (2018) compared buprenorphine subcutaneous depot (SC-BPN) injected weekly/monthly to buprenorphine/naloxone sublingual (SL-BPN/NX) daily.(222) Results indicate SC-BPN was non-inferior to SL-BPN/NX for treatment retention and response rate, but SC-BPN was more effective for reducing opioid consumption verified by opioid-negative urine samples. An RCT by Rosenthal et al. (2016) found buprenorphine 6-month implant was more effective than buprenorphine/naloxone sublingual.(241) However, sensitivity analyses produced inconsistent results and external validity concerns due to the inclusion requirement that patients be abstinent for 90 days and stable on ≤8 mg buprenorphine/naloxone SL for at least a week, which may not reflect the standard OUD population. Marketing and manufacturing for the 6-month implant have since been discontinued.(222, 241)

Despite the lack of evidence to recommend specific formulations or routes of delivery, any FDA-approved buprenorphine formulation for OUD has significant benefits that outweigh harms for opioid consumption, treatment retention, and relapse prevention. Clinicians should consider multiple factors in selecting the appropriate therapy including a patient's values and preferences, clinical history, and pharmacoeconomics. Some patients may complain about the burden of daily administration, while others may refuse injections. Alternative formulations may be effective for those with concerns for adherence or multiple relapses or overdoses.

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation.(222, 241) The confidence in the quality of evidence was very low. The body of evidence had some limitations including blinding issues, imprecision, and funding exclusively by the manufacturers. The Work Group determined buprenorphine treatment in any form has benefits that outweigh the risks and, depending on a clinician's assessment and a patient's values and preferences, an alternative form or delivery system for buprenorphine may be indicated. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

More research is needed on the comparative safety and effectiveness of buprenorphine sublingual with buprenorphine formulations delivered through alternative routes.

Recommendation

19. There is insufficient evidence to recommend for or against oral naltrexone for the treatment of opioid use disorder.
    (Neither for nor against | Reviewed, Not changed)

Discussion

An RCT by Sullivan et al. (2019) examined the efficacy of naltrexone XR versus oral naltrexone for OUD, including opioid consumption and treatment retention.(237) Naltrexone XR (n=28) versus oral naltrexone (n=32) resulted in no difference in opioid-positive UDT (p=0.57). With regards to treatment retention, the 95% confidence interval (CI) favored naltrexone XR (hazard ratio 2.18; 95% CI: 1.07 to 4.43); however, the study was very low quality due to serious limitations and imprecision.(237) In one small RCT by Mokri et al. (2016) where oral naltrexone (n=51) was compared to buprenorphine/naloxone (n=51), the duration of verified initial opioid abstinence days was inconclusive (p=0.205).(242) Outcomes for the number of opioid-negative UDT favored buprenorphine/naloxone (p=0.049); however, the quality of evidence was very low.(242)

Benefits and harms of treatment are balanced, as there are few side effects and adverse outcomes with naltrexone. Patients should be abstinent from opioid use within the prior 7 – 10 days, and potentially longer if using a long-acting opioid such as buprenorphine or methadone. There are likely large variations in patient preferences and values regarding naltrexone versus other treatment options. The use of injectable naltrexone may be preferred when adherence to oral naltrexone is a concern. The use of an injectable will reduce pill burden and adherence, which may improve outcomes to treatment. Some patients may not want a monthly injection that requires coming to a healthcare facility, and some may not be interested in agonist treatment with buprenorphine or methadone. Additionally, when access to a clinic is limited (e.g., geographic location, during a pandemic), or if financial resources limit access to injectable naltrexone, oral naltrexone may be preferred.

As this is a *Reviewed, Not changed* recommendation, the Work Group systematically reviewed evidence related to this recommendation (237, 242) and considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG. The Work Group's confidence in the quality of the evidence was very low. Benefits and harms/burdens are balanced; although there are no significant documented benefits, the harms of negative side effects and adverse events are minimal. Patient values and preferences largely varied due to potential aversion to injections and limited access to clinics for injectable naltrexone. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

d. Opioid Use Disorder – Psychosocial Interventions

Recommendation

20. For patients receiving medication treatment for opioid use disorder, there is insufficient evidence to recommend for or against any specific psychosocial interventions in addition to addiction-focused medical management.
    (Neither for nor against | Reviewed, Amended)

Discussion

The efficacy of MOUD in reducing illicit opioid use and retaining patients in treatment (the two critical outcomes) has been amply demonstrated in controlled trials over several decades.(243) Nevertheless, as with many treatments in medicine, outcomes with MOUD are imperfect. Thus, interest continues in determining if adding various psychosocial or behavioral interventions to medications will further improve outcomes and in determining if any specific psychosocial or behavioral interventions are superior to others in this context.

Three RCTs examining adding individual drug counseling (IDC),(244) CBT,(245) or contingency management (CM) (61) to physician medical management of buprenorphine treatment did not enhance effects on reducing illicit opioid use or improving treatment retention. Two studies suggest that adding a computerized psychosocial intervention based on the CRA and CM to buprenorphine treatment may improve outcomes, but participants in these studies did not receive physician medical management, and the control conditions did not adequately balance the experimental conditions for time and attention.(246, 247)

An SR and meta-analysis of 22 studies by Ainscough et al. (2017) examining CM to reduce illicit drug use among individuals receiving MOUD found CM was quite efficacious for reducing non-opioid drug use but

not for reducing illicit opioid use.(248) Nevertheless, two individual randomized trials conducted in China that were not included in Ainscough et al. (2017) showed significant benefit of CM in increasing the percentage of opioid negative urine specimens and retention in treatment among patients receiving methadone treatment.(249, 250) Thus, the efficacy of CM for improving opioid use outcomes in methadone treatment remains uncertain. A more recent meta-analysis found that the addition of CM to OAT for OUD improved treatment retention, whereas no other psychosocial intervention improved retention compared to medication alone.(251) This meta-analysis was not included in this CPG's evidence review, and therefore not used in determining the strength of this recommendation.

A small randomized trial by Barry et al. (2019) comparing CBT to IDC in patients with chronic low back pain on methadone treatment for OUD suggested CBT may have led to modest reductions in illicit opioid use; however, the experimental group started with a lower baseline level of use.(252)

A larger randomized trial by Pan et al. (2015) compared CBT plus standard methadone treatment to standard treatment alone (monthly health education and voluntary counseling).(253) Participants randomized to CBT had slightly less illicit opioid use but showed no differences in treatment retention, and the conditions were not balanced for time and attention. An RCT by Marsden et al. (2019) randomized participants on either buprenorphine or methadone who had evidence of ongoing illicit drug use to receive either a toolkit of psychological interventions, which included CM, TSF, and behavioral activation tailored to the individual participant plus treatment as usual (TAU) or simply to receive TAU (i.e., biweekly counseling sessions).(254) A slightly higher (but still small) proportion of participants receiving the psychological interventions achieved a month of self-reported abstinence from opioids partially confirmed by urine toxicology compared to participants receiving TAU. That difference barely achieved statistical significance and, once again, the conditions were not balanced on time and attention.

Finally, in a study of oral naltrexone treatment for OUD, participants were randomly assigned in a 2 X 2 design to one of four conditions: (1) behavioral naltrexone treatment plus one injection of naltrexone XR; (2) behavioral naltrexone treatment plus placebo injection; (3) compliance enhancement plus active injection; (4) compliance enhancement plus placebo injection.(255) Behavioral naltrexone treatment consisted of an amalgamation of psychosocial interventions including CM, motivational techniques, and cognitive behavioral techniques delivered by a psychologist. Compliance enhancement consisted of medical management, health education, and supportive psychotherapy delivered by a psychiatrist. The main outcome of interest was treatment retention since illicit opioid use was very low for all retained participants. For participants with low severity of heroin use, retention was better in the behavioral naltrexone plus active injection condition; for participants with high severity, there was no differential retention by treatment condition.(255)

The quality of evidence regarding the efficacy of any specific psychosocial intervention for patients on MOUD was very low because of high attrition rates and weak control conditions in many of the studies. Harms and benefits of psychosocial treatment added to MOUD were balanced because, although the evidence for benefit is scant, potential harms from these types of psychosocial interventions are minimal.

Patient preferences may vary largely for being offered the addition of psychosocial interventions to MOUD since some patients are not interested in receiving the psychosocial interventions, whereas others seek

them out. In general, patients who do not wish to receive a psychosocial intervention should not be required to do so.

As this is a *Reviewed, Amended* recommendation, the Work Group systematically reviewed evidence related to this recommendation (248, 252-255) and considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(61, 244-247) The Work Group's confidence in the quality of the evidence was very low. The extant body of evidence indicates that for patients receiving MOUD, especially under careful medical management, no additional psychosocial treatment should be required to continue receiving medication for OUD. The body of evidence also showed no strong evidence that the addition of psychosocial treatments leads to better results for the critical outcomes of illicit opioid use and treatment retention. The addition of psychosocial interventions might lead to improvements in other outcomes (e.g., use of other illicit substances, employment, and interpersonal relationships). The current comparative effectiveness research does not show the superiority of any specific psychosocial intervention over another for patients receiving MOUD. Harms and benefits were balanced given the known benefits and minimal documented harms. Patient values and preferences vary largely. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Since multiple studies have compared existing psychosocial interventions in the context of MOUD and none seem superior to any other, future work comparing existing interventions is probably not warranted. Psychosocial interventions that have not yet been developed and that would be patient-centered, acceptable to patients, and relatively easy to deliver with minimal training might be worth testing. Also, the impact of existing psychosocial interventions on secondary outcomes (e.g., improvement in co-occurring psychiatric disorders, employment, physical health, and interpersonal relations) would be worth exploring.

Recommendation

21. 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.
    (Neither for nor against | Not reviewed, Amended)

Discussion

This recommendation is carried forward from the 2015 VA/DoD SUD CPG, and this topic was not included in this CPG's evidence review because of evidence already showing outcomes are very poor for patients with OUD treated without medication. Since there is no evidence to indicate any psychosocial intervention is efficacious in the absence of MOUD, it is tautological to state that there is no evidence supporting one psychosocial intervention over another in this context. Also, no studies compare one psychosocial intervention to another in the absence of medication treatment.

There is a potential of harm in using psychosocial interventions without medication to treat OUD, but if medication treatment is unacceptable or unavailable, the harms or benefits of using any specific psychosocial intervention are balanced since psychosocial interventions do not in and of themselves pose any serious risks; however, as noted above, they are unlikely to confer many benefits in this context. Despite the robust evidence for medication treatment, some patients may refuse medications. In these

circumstances, consider providing whatever psychosocial interventions are acceptable to the patient, assuming the provider has the skill and knowledge to deliver the selected intervention.

There have been no studies comparing various psychosocial interventions for OUD without also providing MOUD. These studies have not been performed because treatment without medication has been demonstrated to be ineffective. Therefore, in situations in which medications for OUD are unacceptable or unavailable, there is no evidence to recommend for or against any specific psychosocial intervention.

As this is a *Not reviewed, Amended* recommendation, the Work Group considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(256-259) The Work Group's confidence in the quality of the evidence was very low due to the lack of literature on this topic. The benefits and harms were balanced because although the harms are minimal, there is low evidence for benefit without MOUD. Patient values and preferences were somewhat varied because some patient populations (e.g., active duty Service Members) may be resistant to MOUD. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Future research on psychosocial interventions for OUD in the absence of medication treatment should not be performed because doing so would be unethical.

e. Cannabis Use Disorder – Pharmacotherapy

Recommendation

22. There is insufficient evidence to recommend for or against the use of pharmacotherapy in the treatment of cannabis use disorder.
    (Neither for nor against | Reviewed, Not changed)

Discussion

While some patients seek pharmacologic assistance in reducing or abstaining from cannabis use, there is little to no evidence suggesting medication is effective. Drug trials examining candidate therapies in the cannabis literature are characterized by small sample sizes, short duration, high dropout rates, and absence of treatment effect attributable to the intervention drug. Some form of psychotherapy was provided in most of these studies to treatment and control groups, and the intensity of cannabis usage declined in both groups at similar rates throughout the studies.

Two recent SRs failed to show evidence for effective pharmacotherapy. One SR across 26 trials failed to show that medication increased abstinence or reduced cannabis use, including selective serotonin reuptake inhibitors (SSRIs) and cannabinoids.(260) Another SR, Nielsen et al. (2019), reviewed 21 RCTs and found synthetic delta 9-tetrahydrocannabinol, SSRIs, mixed action antidepressants, buspirone, and N-acetylcysteine were likely ineffective for the critical outcome of abstinence at the end of treatment.(261)

Several RCTs also failed to show a primary treatment effect of drug versus placebo. These trials included one study each for bupropion sustained-release, nefazodone, fluoxetine,(95) buspirone,(262) and atomoxetine.(263, 264) Only a single gabapentin study demonstrated meaningful improvements in cannabis use and withdrawal symptoms, but the sample size was small (n=50).(265) Fluoxetine showed efficacy for depressive symptoms but did not improve cannabis use measures.(95)

In addition, an SR from the VA Evidence Synthesis Program (ESP) reviewed 12 trials and found antidepressants as a class were less likely than placebo to achieve abstinence, and there was no difference as it related to a reduction in overall cannabis use or retention in treatment.(266) Further, findings for all other pharmacotherapies were reported as either insufficient or were not identified in the current literature.(266) While not reviewed by the Work Group, one small RCT with limited follow up utilizing cannabidiol at two different doses showed some promise.(267)

As this is a *Reviewed, Not changed* recommendation, the Work Group systematically reviewed evidence related to this recommendation and considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(95, 262-265) The Work Group's confidence in the quality of the evidence was very low. The body of evidence has limitations related to small sample sizes, short duration, high dropout rates, and absence of treatment effect attributable to the intervention drug. The existing evidence did not favor any medication for the treatment of cannabis use disorder. The benefits and harms were balanced because the Work Group found no benefit and no significant harms (except for one minimal harm, which is that antidepressants may negatively impact abstinence). Patient values and preferences varied somewhat, as some patients may not be open to medication management. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

The Work Group noted there is a need for further research to test new agents, including cannabidiol, to identify effective pharmacologic interventions for the treatment of cannabis use disorder. In addition, although cannabis laws are changing, active duty Service Members are prohibited from using or possessing hemp, cannabinoids, CBD, and all other cannabis-related products.

f. Cannabis Use Disorder – Psychosocial Interventions

Recommendation

23. For patients with cannabis use disorder, we suggest one of the following interventions as initial treatment, considering patient preference and availability:
    - Cognitive behavioral therapy
    - Motivational enhancement therapy
    - Combined cognitive behavioral therapy/motivational enhancement therapy

    (Weak for | Reviewed, Amended)

Discussion

The 2015 VA/DoD SUD CPG suggested using CBT, MET, and combined cognitive behavioral therapy/motivational enhancement therapy (MET-CBT). After further reviewing the literature, the Work Group chose to carry forward this recommendation and suggest these interventions given their effectiveness. The interventions considered did not demonstrate superiority.

The Work Group reviewed three relevant RCTs: Buckner et al. (2019),(268) Litt et al. (2020),(269) and Walker et al. (2015).(270) Buckner et al. (2019) compared MET-CBT with Integrated Cannabis and Anxiety Reduction Treatment (ICART).(268) In this study, the ICART group did not separate from the MET-CBT in outcomes for patients with a comorbid anxiety disorder.(268) This was a small study that looked only at patients with cannabis use disorder and an anxiety disorder, and therefore, we could not generalize the results to patients with cannabis use disorder.

Litt et al. (2020) compared MET-CBT to MET-CBT and CM, finding slight benefits to the addition of CM.(269) In a separate treatment arm, the study also considered Individualized Assessment and Treatment Program (IATP), a form of CBT individualized to a person's coping skills. The study showed IATP was slightly superior to MET-CBT. Finally, the authors found the addition of CM to IATP did not improve outcomes. This was a low quality study based on the small sample size.

Walker et al. (2015) compared MET-CBT alone with MET-CBT with added Maintenance Check-ups (MCU) at one and four months.(270) The group receiving MCUs showed slight benefit at three months; however, there was no benefit at nine months. Any benefit was short term. This study also had a small sample size.

Since none of the experimental treatments were superior to CBT, MET, or MET-CBT, and given the increased use of resources, the Work Group does not recommend adding any of these treatments. Based upon the older literature, the Work Group continues to recommend CBT, MET, and MET-CBT. Given the equivalence of these treatments, the Work Group does not recommend one treatment over another.

There is some variation in patient preferences given that many prefer to avoid more intensive behavioral therapies despite their effectiveness. For these patients, MET is appropriate. There were also some equity considerations given that these therapies are less available in rural settings and more accessible in residential settings. The Work Group also considered the career implications (e.g., administrative separation) in active duty populations using cannabis.

As this is a *Reviewed, Amended* recommendation, the Work Group systematically reviewed evidence related to this recommendation.(268-270) The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including small population sizes and heterogeneity of the populations studied. The benefits (e.g., improved consumption outcomes) outweighed the potential harms, which were minimal. Patient values and preferences varied somewhat. Thus, the Work Group decided upon a *Weak for* recommendation.

Given the growing incidence of cannabis use disorder, the Work Group believes that further research is indicated into effective treatment interventions.

Recommendation

24. We suggest against the use of a brief intervention (i.e., 60 minutes or less) for the treatment of cannabis use disorder.
    (Weak against | Reviewed, New-added)

Discussion

Imtiaz et al. (2020) showed that while brief interventions (BIs) have succeeded in addressing problematic alcohol use, evidence suggests BIs do not provide any benefit for individuals with cannabis use disorder.(271) A BI was defined as an intervention that lasts ≤60 minutes and occurs in two or fewer sessions. This study did not consider interventions >60 minutes, and this recommendation does not address other therapies lasting >60 minutes.

In addition to the evidence showing the ineffectiveness of BIs, they require substantial resources if applied across large groups of patients. Brief interventions generally explore methods to make problematic use

less problematic without abstinence. As such, BIs may make an individual with cannabis use disorder more resistant to treatment given the focus on less problematic use. Additionally, many patients will avoid this intervention, particularly in active duty personnel whose careers may be implicated. Finally, BIs are not always feasible given the lack of training for many providers. For these reasons, clinicians should forego BIs in favor of more traditional interventions.

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation.(271) The Work Group's confidence in the quality of the evidence was very low. The lack of efficacy, limited training for clinicians, and inappropriate resource allocation also make BIs inappropriate and result in potential harms outweighing potential benefits (as the Work Group did not identify evidence of any benefit). Patient values and preferences varied somewhat because some patients may not be receptive to BIs in certain settings. Thus, the Work Group decided upon a *Weak against* recommendation.

g. Stimulant Use Disorder – Pharmacotherapy

Recommendation

25. There is insufficient evidence to recommend for or against the use of any pharmacotherapy for the treatment of cocaine use disorder or amphetamine/methamphetamine use disorder. **(Neither for nor against | Reviewed, Amended)**

Discussion

The incidence of amphetamine use disorder, methamphetamine use disorder, and cocaine use disorder (and other stimulants) is increasing in the U.S., and it is critically important to identify pharmacotherapy approaches for their treatments.

The 2015 VA/DoD SUD CPG noted the evidence did 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. Several small studies have shown mixed results, with some studies showing modest benefits, while some have shown no benefit.(272, 273) Indeed, evidence suggests disulfiram worsens cocaine use disorder at some doses, while cocaine use decreases at a dose of 250 mg/day.(272, 274-276)

The 2015 VA/DoD SUD CPG noted that given the wide variation in the studies, there was insufficient evidence to recommend 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 prior CPG noted providers should consider the likelihood of misuse and diversion in patients receiving methylphenidate, dexamphetamine, and mixed amphetamine salts.

Some RCTs have explored the use of topiramate to decrease cocaine use. One study showed a decrease in use compared to placebo,(277) while another study showed no difference in cocaine use.(278) One study showed that there were no improvement in the rate of abstinence in methamphetamine use disorder with the use of topiramate compared to placebo.(279)

Some emerging literature did not meet this CPG's inclusion criterion as it did not examine the comparative effectiveness of pharmacotherapy to placebo and/or included participants with multiple diagnoses (e.g., cocaine use disorder and OUD). For example, a multi-centered, double-blind, placebo-controlled study sought to examine the safety and effectiveness of buprenorphine + naloxone sublingual provided after administration of extended-release injectable naltrexone to reduce cocaine use in participants who met DSM-IV criteria for cocaine dependence and past or current opioid dependence or abuse.(280) The study found no group differences between groups for the primary outcomes (UDT-corrected, self-reported cocaine use during the last four weeks of treatment). Longitudinal analysis of urine drug screen data during the evaluation period using generalized linear mixed equations found a statistically significant difference between higher dose buprenorphine and placebo. The authors concluded that buprenorphine/naloxone, used in combination with naltrexone, may be associated with reduced cocaine use among persons who meet criteria for cocaine use disorder and who have prior or current OUD. Other studies were considered but were also not included in this CPG's evidence review (and therefore not used in determining the strength of this recommendation) as they did not meet the criteria for inclusion.(281-285)

The 2021 VA/DoD SUD CPG examined a VA ESP SR that assessed pharmacologic interventions on methamphetamine/amphetamine use disorder outcomes.(286) This SR assessed the efficacy of various pharmacotherapies in the management of methamphetamine or amphetamine use disorder and concluded that most medications evaluated for methamphetamine/amphetamine use disorder have not shown a statistically significant benefit. The SR authors also mentioned that there is low strength evidence that methylphenidate may reduce use. Of note, the review consisted of only fair quality studies other than an RCT that compared the medications baclofen and gabapentin in reducing use. This RCT showed there is no difference between baclofen and gabapentin for the longest days of reported abstinence, percentage of negative urinalysis, and retention of study participants. The study was limited by low sample size and few comparators, and the GRADE of evidence for the critical outcomes was very low.

The Work Group examined the comparative effectiveness of medications to treat amphetamine use disorder, methamphetamine use disorder, and cocaine use disorder, and did not consider recent literature examining potential treatments compared to placebo. For example, in a very small, open-label study, injectable naltrexone and bupropion were tested as an intervention for patients with severe methamphetamine use disorder, and there were indications that the combined treatment demonstrated treatment "response".(287)

It is important to note a recently published study, not reviewed by the Work Group and, therefore, not used in determining this recommendation's strength, found there may be some benefit in combined treatment of methamphetamine use disorder using injectable naltrexone and bupropion.(288) In 2021, this multisite, double-blind, two-stage, placebo-controlled trial with the use of a sequential parallel comparison design to evaluate the efficacy and safety of extended-release injectable naltrexone (380 mg every 3 weeks) plus oral extended-release bupropion (450 mg/day) in adults with moderate or severe methamphetamine use disorder examined outcomes of a "response," defined as at least three methamphetamine-negative UDT in a defined time period.(288) Two stages occurred, where Stage 1 participants were randomized to placebo or pharmacotherapy combination, and Stage 2 consisted of randomization of treatment non-responders in Stage 1. The weighted average response across the two stages was 13.6% with naltrexone-bupropion and 2.5% with placebo, for an overall treatment effect of

11.1% (p<0.001). Adverse events with naltrexone-bupropion included gastrointestinal disorders, tremor, malaise, hyperhidrosis, and anorexia. Serious adverse events occurred in 1 of 109 participants who received naltrexone-bupropion in Stage 1, in 4 of 294 who received placebo in Stage 1 and in 4 of 114 who received naltrexone-bupropion in Stage 2, and in 4 of 111 who received placebo in Stage 2. The authors concluded, "Among adults with methamphetamine use disorder, the response over a period of 12 weeks among participants who received extended-release injectable naltrexone plus oral extended-release bupropion was low but was higher than that among participants who received placebo."(288)

There is wide inconsistency in the evidence supporting pharmacotherapy for the treatment of amphetamine use disorder, methamphetamine use disorder, and cocaine use disorder. Also, there is large variation in patient values and preferences in the treatment of these conditions. In addition, the Work Group considered the unique population of patients with methamphetamine use disorder, amphetamine use disorder, and cocaine use disorder. This is a population that often uses other illicit substances (polysubstance use), making recommendations for pharmacotherapy difficult for methamphetamine use disorder, amphetamine use disorder, or cocaine use disorder in isolation.

As this is a *Reviewed, Amended* recommendation, the Work Group systematically reviewed evidence related to this recommendation (286) and considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(273-279) The Work Group's confidence in the quality of the evidence was very low. The body of evidence has some limitations including very small sample sizes and imprecision. The benefits, including weak difference for abstinence and no difference for retention outcomes, and harms/burden (minimal) were balanced. Patient values and preferences largely varied. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

h. Stimulant Use Disorder – Psychosocial Interventions

Recommendation

26. For patients with cocaine use disorder, we recommend one or more of the following interventions as initial treatment, considering patient preference and availability:
    - Cognitive behavioral therapy
    - Recovery-focused behavioral therapy (i.e., individual drug counseling and community reinforcement approach)
    - Contingency management in combination with another behavioral intervention considering patient preference and availability

    (Strong for | Not reviewed, Amended)

Discussion

Evidence suggests CBT is effective for the treatment of cocaine use disorder.(289-291) In a recent meta-analysis of CBT versus other treatments in patients also receiving pharmacotherapy, adding CBT to usual care significantly improved cocaine use outcomes in patients with cocaine use disorder, although it was less effective when compared to other evidence-based interventions such as CM.(292) This meta-analysis was not included in this CPG's systematic evidence review, as it was published after this review was conducted. Therefore, it was not considered when determining this recommendation's strength.

The combination of IDC, which is based on a 12-step addiction treatment model, plus group drug counseling, improved cocaine use outcomes over group drug counseling only.(293) Also, it was superior to the combination of individual cognitive therapy plus group drug counseling and the combination of an individual psychodynamic approach plus group drug counseling in one large, carefully conducted multi-site study.(293)

Community reinforcement approach, 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., drug counseling and CRA without voucher incentives) in several studies.(294-296) In some studies, the combination of CM and other behavioral interventions, such as CRA or CBT, has been more effective than comparison conditions.(289, 297) 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.(298)

Contingency management has the strongest evidence of effectiveness for cocaine use disorder when used adjunctive to another psychosocial intervention.(289, 299, 300) Another recent SR found CM to be consistently more effective than CBT during treatment, with less evidence of superiority during post-treatment follow-ups.(301) Extending the duration in which reinforcement for abstinence is provided extends the positive effects of CM,(302) but positive effects generally deteriorate fairly rapidly after the intervention has ended in most studies. However, at least one study found evidence of sustained positive effects for 12 months after the end of CM.(303)

Treatment effects are generally much larger when abstinence (as opposed to attendance) is reinforced, although this may not be the case for patients with a better prognosis who are cocaine abstinent when they enter treatment.(304) Higher monetary value reinforcers produce higher rates of cocaine abstinence,(305) particularly in those with more severe cocaine problems.(304) Prize-based CM interventions, in which the amount of the reinforcement varies by chance, may be more cost-effective than fixed-value reinforcement.(306, 307)

The primary concerns regarding CBT, CRA, IDC, and CM include considerable training to implement with fidelity (CBT, CRA, IDC) and the resource-intensive delivery (CM, CBT, CRA, IDC). For example, CM 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 indicated CM is feasible to deliver within VA treatment programs.(308, 309) Finally, the research is based mostly on studies in which interventions were delivered to individual patients, whereas most SUD treatment in the VA and DoD is delivered in groups.

As this is a *Not reviewed, Amended* recommendation, the Work Group considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(289-291, 293-296, 299-307) The Work Group's confidence in the quality of the evidence was moderate. The benefits (i.e., significantly improved outcomes) outweighed the potential harms (i.e., training required for providers and frequent urine tests for CM). Patient values and preferences varied somewhat, due to the variability in patient interest in psychosocial interventions, and some providers may question the appropriateness of the use of resources for CM and/or may be opposed to the concept of CM. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

27. For patients with amphetamine/methamphetamine use disorder, we suggest offering contingency management as initial treatment in combination with another behavioral intervention, considering patient preference and availability.
    (Weak for | Not reviewed, Amended)

Discussion

There is considerably less evidence concerning effective treatments for stimulant disorders other than cocaine use disorder. One SR found that behavioral interventions, including CBT, CBT plus MI, and MI alone, were not more effective than passive or minimal interventions with regard to non-cocaine stimulant consumption outcomes. However, high intensity or combination treatments, such as CBT with additional focus on triggers and other issues commonly experienced by LGBTQ individuals, CM plus CBT, CM plus TAU, and CM plus placebo, did produce better stimulant use outcomes than single active treatments (i.e., CBT or TAU).(310) It should be noted that most of these high-intensity or combination interventions included CM, so the positive effect identified may be for CM over other active behavioral interventions.

A recent SR of psychological treatments for methamphetamine use concluded that more intensive interventions, including the Matrix Model and the combination of MI and CBT, produced greater decreases in methamphetamine use than standard care and less intensive treatments.(311) This SR was not included in this CPG's systematic evidence review (as it was a narrative synthesis rather than a meta-analysis), and therefore, did not impact the strength of this recommendation.

The primary concerns regarding the interventions CBT, CBT + MI, and CM + CBT include considerable training to implement with fidelity and the resource-intensive delivery. For example, CM 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 indicated CM is feasible to deliver within VA treatment programs.(308, 309) Finally, the research is based mostly on studies in which interventions were delivered to individual patients, whereas most SUD treatment in the VA and DoD is delivered in groups.

As this is a *Not reviewed, Amended* recommendation, the Work Group considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(310) The Work Group's confidence in the quality of the evidence was low. The benefits outweighed the potential harms (i.e., frequent urine tests). Patient values and preferences varied somewhat, due to the variability in patient interest in and reception to CM when combined with TAU or other behavioral interventions and some providers may question the appropriateness of the use of resources for CM and/or may be opposed to the concept of CM. Thus, the Work Group decided upon a *Weak for* recommendation.

E. Group Mutual Help Involvement

Recommendation

28. For patients with alcohol use disorder 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 availability:
    - Peer linkage
    - Network support
    - 12-step facilitation

    (Strong for | Reviewed, New-replaced)

Discussion

Several interventions may increase attendance and participation in mutual help programs and other recovery-oriented social support programs and, in some cases, may also improve alcohol use outcomes: peer linkage, network support (NS), and TSF. Studies conducted before 2015 support the efficacy of these interventions.(312)

This recommendation is based primarily on higher quality studies conducted before 2015, which were included in the 2009 and 2015 VA/DoD SUD CPGs. The most recent systematic review of AA and interventions designed to increase participation in mutual help programs is a Cochrane SR, that includes some of these older studies.(312) This SR found that manualized AA and interventions to increase participation in mutual help programs produced higher rates of continuous alcohol abstinence at 12, 24, and 36 months than various comparison interventions, as well as more days of alcohol abstinence at 24 and 36 months.

An earlier SR by Humphreys et al. (2014) (313) examined six RCTs in which AA facilitation interventions were compared to other active treatment interventions for AUD, including MET, CBT, supportive-expressive therapy, case management, and relapse prevention. The AA facilitation interventions in this SR included TSF (Project MATCH Research Group, 1997) and NS.(314) The results indicated that AA facilitation interventions significantly increased days abstinent at three and 15-month follow-ups, relative to the comparators.

The first manualized intervention developed to increase participation in mutual help programs was TSF, which has also been the most studied of these interventions. This 12-session intervention helps patients complete the initial steps of 12-step programs, and seeks to reduce barriers to attending mutual help meetings. Systematic reviews have supported the efficacy of TSF for AUD.(312, 313)

Peer linkage, which is provided over three sessions, consisted of information about the 12-step (i.e., AA/NA) 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.(315) 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.(315, 316) Moreover, the peer linkage referral condition also produced greater reductions in alcohol use severity

from baseline to 12 months and higher rates of abstinence from alcohol over the follow-up than standard referral.(316)

Litt et al. (2007) adapted TSF to develop NS, which stresses changing one's broader social network to be more supportive of abstinence and advocates involvement in 12-step programs.(314) Alcoholics Anonymous' 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 are explored, particularly for patients who will not attend mutual help programs. The RCT comparing NS to case management found increased social support for abstinence, through an increase in abstinent friends, and lower rates of drinking in NS relative to case management.(314) Concerning 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 and alcohol use, relative to case management, was sustained.(317) This study was included in the Kelly et al. (2020) Cochrane SR.(312)

A second study by Litt et al. (2016) compared NS to CBT in individuals with AUD.(318) It found NS yielded better outcomes than CBT on the proportion of days abstinent, drinking consequences, and AA attendance over a 27-month follow-up. The two conditions did not differ on rates of 90-day abstinence, heavy drinking days, or drinks per drinking day.(318) Mediation analyses indicated that the positive effects of NS relative to CBT were accounted for by increases in the proportion of non-drinkers in the social network and attendance at AA.(318) This study was also included in the Kelly et al. (2020) Cochrane SR.(312)

Peer linkage is less resource-intensive than TSF or NS, and access to any of these interventions is limited. On the other hand, NS may be more appropriate for patients who do not want to go to AA since it can be focused on other sources of recovery support. Finally, a referral to AA, which is an abstinence-oriented approach to recovery, is not appropriate for patients with a goal of controlled drinking.

Given the geographic mobility of active duty Service Members across the country and the world, facilitating 12-step meeting attendance can be a particularly important skill for clinicians working with the active duty population.

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation (312) and considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(313) The Work Group's confidence in the overall quality of the evidence was moderate. Of the three interventions that are suggested, TSF has the largest evidence base. Notably, most of the RCTs in which TSF, NS, and peer linkage interventions have been tested have included active comparator conditions, including CBT, MET, case management, and various forms of standard care, which increases the confidence in the impact of these interventions. For patients with AUD, the evidence base is strongest for the positive impact of these interventions on rates of continuous alcohol abstinence. Evidence for other alcohol outcomes (e.g., frequency of drinking) is almost as strong. The benefits (i.e., improved drinking outcomes, increased attendance at AA and other 12-step meetings) outweighed the potential harm of adverse events, which was small. Patient values and preferences vary largely since many individuals with SUD do not want to attend 12-step meetings. Thus, the Work Group decided upon a *Strong for* recommendation.

To this point, there have been no studies comparing TSF, peer linkage, and NS. Additional studies that compare TSF, peek linkage, and NS are warranted.

Recommendation

29. For patients with drug use disorders in early recovery or following relapse, we suggest promoting active involvement in group mutual help programs using one of the following systematic approaches, considering patient preference and availability:
    - Peer linkage
    - 12-step facilitation

    (Weak for | Reviewed, New-replaced)

Discussion

There is less evidence regarding the impact of interventions designed to increase involvement in group mutual help programs on drug use outcomes. Since 2015, two studies included in an SR by Hides et al. (2019) (319) and an RCT by Azkhosh et al. (2016) (320) have examined interventions of this sort.

Two RCTs within this SR compared TSF with integrated CBT (iCBT) for substance use and adherence.(319) This SR found iCBT produced more abstinent days than TSF, with no differences in treatment attendance or retention.(319) However, the strength of the evidence was very low, due to small sample sizes and poor methodological quality.

An RCT conducted in Iran, Azkhosh et al. (2016), compared 12-step Narcotics Anonymous (12SNA), an intervention designed to increase participation in NA, to acceptance and commitment therapy (ACT), and MMT on quality of life (psychological well-being).(320) It found the treatment that promoted 12-step involvement produced higher quality of life scores than MMT, but the strength of the evidence was very low.(320)

12-step facilitation was compared to standard counseling for stimulant-dependent patients maintained on methadone.(321) Results indicated that TSF produced lower rates of cocaine use and greater attendance at 12-step meetings than standard counseling.

In addition to improved alcohol use outcomes, the peer linkage referral intervention produced greater reductions in drug use severity from baseline to 12 months and higher rates of abstinence from drugs over the follow-up than standard referral.(316)

Peer linkage is less resource-intensive than TSF, and access to any of these interventions is limited. Finally, a referral to AA or NA, which are abstinence-oriented approaches to recovery, is not appropriate for patients with a goal of controlled drug use.

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation (319, 320) and considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(321) The Work Group's confidence in the overall quality of the evidence was low. Most of the work with these interventions has focused on AUD rather than other drug use disorders. The evidence is weak for other SUDs. The benefits (i.e., improved drug use outcomes, increased attendance at 12-step meetings) outweighed the potential harm of adverse events, which was small. Patient values and

preferences vary largely since many individuals with SUD do not want to attend 12-step meetings. Thus, the Work Group decided upon a *Weak for* recommendation.

To this point, there have been no studies comparing TSF, peer linkage, and NS. In addition, most of the research with these interventions has focused on patients with AUD. Additional studies that compare TSF, peek linkage, and NS are warranted, as are studies with patients who have drug use disorders.

F. Mindfulness-based Therapies

Recommendation

30. There is insufficient evidence to recommend for or against mindfulness-based therapies for the treatment of substance use disorders.
    (Neither for nor against | Reviewed, New-added)

Discussion

While an SR by Cavicchioli et al. (2018) included 25 RCTs, only eight RCTs were specific to mindfulness-based relapse prevention (MBRP) or ACT.(322) These studies compared MBRP or ACT to CBT, MMT, or TAU. The confidence in the quality of evidence for critical outcomes (i.e., abstinence, attrition, quality of life) was very low. There was no difference in outcomes when ACT was compared to CBT, health education, MMT, or TAU. There was no difference when ACT + MMT was compared to MMT or CBT.

The Work Group reviewed eight additional RCTs. Abed et al. (2019) compared MBRP + MMT to MMT.(323) The quality rating was poor (randomization and allocation inadequately reported, no ITT analysis) and MBRP + MMT was favored over MMT. Black and Amaro (2019) compared moment-by-moment in women's recovery (a mindfulness-based intervention adapted to support women with SUD in a residential setting) to health education.(324) The quality rating was good (low risk for bias of randomization, ITT analysis completed). There was no difference between groups. This study was conducted in a residential program. Davis et al. (2018) compared MBRP to TAU.(325) The overall quality rating was good (low risk of bias for randomization, ITT analysis completed). Mindfulness-based relapse prevention was favored over TAU. This study was conducted at a residential program.

Foroushani et al. (2019) compared MBRP + MMT to MMT.(326) The quality rating was poor since randomization and allocation were inadequately reported and no ITT analysis was reported. In this study, MBRP + MMT was favored over MMT. Machado et al. (2019) compared MBRP to TAU.(327) The quality rating was poor (randomization and allocation inadequately reported, no ITT analysis) and there was no difference between the groups. Yaghubi et al. (2017) compared MBRP + MMT to MMT.(328) The quality rating was poor since randomization and allocation were inadequately reported, and no ITT analysis was reported. When looking at the impact of MBRP on impulsivity and relapse for patients on methadone, MBRP + MMT was favored over MMT.

Yaghubi et al. (2018) compared MBRP + MMT to MMT.(329) The quality rating was poor since randomization and allocation were inadequately reported and no ITT analysis was reported. When looking at the impact of MBRP on quality of life and cravings, MBRP + MMT was favored over MMT. Zgierska et al. (2019) compared mindfulness-based relapse prevention-alcohol dependence + TAU to TAU.(330) The

quality rating was poor as randomization and allocation were inadequately reported. Additionally, no ITT analysis was reported. There was no difference between the groups.

The overall strength of the evidence for MBRP or ACT was very low. There was a high risk of bias in several studies. Some small RCTs favored MBRP, but there was not enough evidence to make a recommendation for the addition of MBRP in SUD treatment. Although the benefits may slightly outweigh the harms, the current evidence does not support this. In practice, MBRP is used more frequently than the research demonstrated. It may be that research has yet to catch up to practice.

There is some variation in patient values and preferences, as some focus group participants reported utilizing and benefiting from mindfulness-based treatment activities. Also, some patients may not be comfortable with mindfulness-based approaches, especially those with serious mental illness.(331) Access to trained MBRP providers could also be a barrier to its use.

Mindfulness-based therapy (MBT) programs are used as an adjunctive treatment for various disorders and are sometimes used in the treatment of patients with SUD. While this Work Group determined there was not sufficient evidence to recommend MBT, there is no evidence of harm for patients who indicate interest. Simple mindfulness-based practices such as gratitude practices, journaling, and progressive muscle relaxation may offer the benefit of providing structure to a patient's day and strengthening skills of self-observation and self-inquiry. However, research support is low for the effectiveness of MBT alone or in addition to other therapies for the treatment of SUD.

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed evidence related to the recommendation.(322-330) The Work Group's confidence in the quality of the evidence was very low. The body of evidence had limitations of small sample size, study quality, risk of bias, and loss to follow-up with attrition rate varying from 20 – 50%. The potential benefits (i.e., reduced cravings) slightly outweighed the potential harms. Patient values and preferences vary somewhat. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Further research is indicated for the use of mindfulness-based treatment programs as there is insufficient evidence to recommend for or against these programs. Future studies are needed to clarify which specific therapeutic strategies and mindfulness approaches are effective. The mindfulness approach (i.e., learning to tolerate craving and other types of emotional or cognitive distress) may be beneficial for individuals who do not respond to interventions like CBT that are directed at eliminating craving and other types of distress. Future studies with larger sample sizes are also necessary.

G. Telehealth

Recommendation

31. We suggest using technology-based interventions (e.g., automated text/voice messaging, smartphone apps), in addition to usual care, for alcohol use disorder.
(Weak for | Reviewed, New-added)

32. There is insufficient evidence to recommend for or against using technology-based interventions (e.g., automated text/voice messaging, smartphone apps), in addition to usual care, for substance use disorders other than alcohol use disorder.
(Neither for nor against | Reviewed, New-added)

Discussion

The evidence base consisted of six RCTs that evaluated various technology-based interventions as adjuncts to usual care for adults with SUD. Four RCTs used supportive text messaging (TM) in addition to TAU to support adults receiving treatment for AUD.(332-335) The TM interventions were automated, scripted messages intended to help participants self-monitor substance use behaviors and motivate them to reduce such behaviors. Studies differed in the design, delivery (including the nature of automation), and content of interventions.

These studies examined abstinence, substance use, retention, ED visits, and treatment adherence. Three fair quality RCTs found there was no difference in abstinence measured as any self-reported alcohol consumption,(334) cumulative abstinence,(332) and the number of days to first drink among adults with AUD who received supportive TM monitoring plus TAU compared to TAU only.(332, 333) Similarly, these studies reported on post-treatment substance use and found no difference in average units of alcohol per drinking day or drinking days in the past three months at 3-month and 12-month follow-up. O'Reilly et al. (2019), however, did show that TM plus TAU was associated with fewer overall drinking days and fewer units of alcohol in a drinking day compared to TAU at 6-month follow-up.(334)

These four RCTs all indicated there was no difference between supportive TM and TAU compared to TAU alone in 2-month, 3-month, and 6-month retention among adults with AUD.(332-335) Agyapong et al. (2018) found no difference between supportive TM and TAU alone in ED visits.(332)

Gustafson et al. (2014) enrolled 349 participants with alcohol dependence to receive a smartphone-based application, Addiction-Comprehensive Health Enhancement Support System (A-CHESS) plus TAU versus TAU alone for eight months followed by four months of additional follow-up.(336) Significant increases in abstinence at eight months and 12 months were reported among participants in the A-CHESS group compared to those in TAU alone, in addition to significant reductions in risky drinking days at four months and eight months and overall that favored A-CHESS. Although there were no significant between-group differences in negative consequences of drinking, there were very few events reported in either group, and there were no differences in patient attrition. Most outcomes were supported by low quality evidence (e.g., risky drinking days, abstinence) with very low quality evidence for negative consequences of drinking.

Another study by Rose et al. (2015) compared a fully automated, phone-based Alcohol Therapeutic Interactive Voice Response (ATIVR) in addition to usual care (3-month outpatient CBT) versus usual care-

only for four months followed by eight months of additional follow-up.(337) The ATIVR group had fewer drinking days per week during the intervention compared to the control group supported by low quality evidence, although there were no significant between-group differences in alcohol consumption outcomes at 12 months.

The overall strength of the evidence for most of the outcomes assessing the efficacy of technology-based interventions as an adjunct to usual care was rated low (i.e., substance use, abstinence, retention) to very low (i.e., ED visits, negative consequences of alcohol). These ratings are primarily due to serious limitations in the methodological quality, serious imprecision, and size of the included RCTs. All the studies had some degree of attrition, and some studies also did not report on the blinding of outcome assessors. The overall strength of the evidence was further limited by the small sample sizes of most of the included studies, except for Gustafson et al. (2014), which enrolled over 300 participants.(336)

Despite general consistency in the evidence supporting technology-based interventions in addition to usual care for the treatment of SUD, there is a large variation in patient values and preferences. Focus group participants indicated low trust in some of these technologies; some patients may like the convenience of TM, but others may not appreciate the frequency of TM overall and view it as a potential annoyance. There are few harms associated with supportive TM, and a trend toward some benefit in some of the studies, with only a few statistically significant differences reported. Although digital platforms (e.g., smartphones) and texting are widely available, there are racial, ethnic, and socioeconomic disparities in access to smartphones, broadband, and cell service, as well as geographic variation (e.g., rural communities). These same technologies could be particularly helpful to expand access to SUD care in rural areas, to those who may lack access to transportation or live far away from clinics, or who have other barriers to care such as work or childcare responsibilities during regular business hours.

As Recommendation 31 is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation (332-335) and considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(336, 337) Of note, there are currently FDA-cleared apps in clinical use for the treatment of SUD (e.g., ReSET and ReSET-O),(338) but literature leading to clearance did not meet the inclusion criteria for this CPG's systematic evidence review. The Work Group's confidence in the quality of the evidence was very low, with few significant differences found between groups for most consumption outcomes, retention, and ED visits. The body of evidence was limited by small sample size in most studies, serious limitations in study quality, and serious imprecision. The benefits (e.g., reduced drinking days) outweighed potential harms (e.g., perceived burden of receiving texts). Patient values and preferences largely varied. Thus, the Work Group decided upon a *Weak for* recommendation for AUD.

As Recommendation 32 is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation (332-335) and considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(336, 337) The Work Group's confidence in the quality of the evidence was very low, and studies to date focused only on AUD. The body of evidence was limited by small sample size in most studies, serious limitations in study quality, and serious imprecision. The benefits outweighed potential harms (e.g., perceived burden of receiving texts). Patient values and preferences largely varied. Thus, the Work Group decided upon a *Neither for nor against* recommendation for substance use disorders other than AUD.

Future research is needed on technology-based interventions for non-alcohol SUDs, app-delivered evidence-based SUD treatment, and synchronous (i.e., non-automated) texting support with healthcare providers, as well as technology-supported interventions combined with in-person or telehealth. Additional research could focus on step-based algorithms to personalize treatment and identify patients in need of additional care or a face-to-face appointment.

Recommendation

33. We suggest the use of structured telephone-based care as an adjunct to usual care for substance use disorders.
    (Weak for | Reviewed, New-added)

Discussion

In Timko et al. (2019a), 298 adult patients in two inpatient psychiatry units in the same healthcare system were randomized to an enhanced telephone monitoring (ETM) program plus TAU as compared to TAU alone.(339) Patients had dependence on alcohol (68%, n=202), opioids (11%, n=32), or both alcohol and opioids (21%, n=64). The patients in the ETM group had an initial 50-minute session with an experienced TeleCoach, followed by twelve 15-minute weekly follow-up sessions. The main outcomes studied were readmission to the inpatient psychiatric facility at three and six months. At three months, the ETM group had fewer patients readmitted as compared to TAU alone. However, at six months, there was no difference in readmission rates between the two groups.(339)

Another RCT by Timko and colleagues (Timko et al. [2019b]) (340) examined a low-intensity telephone monitoring program and used a similar approach (initial 30 – 50 minute session inpatient, followed by weekly 15-minute follow-up sessions) as Timko et al. (2019a).(339) In Timko et al. (2019b), 207 patients with a dual SUD and mental health diagnosis were randomized to telephone monitoring in addition to TAU as compared to TAU alone (n=199) to assess the continuation of care and utilization of a 12-step program.(340) The outcomes were days of alcohol use and drug use in the prior 30 days. The telephone monitoring did not impact SUD related patient outcomes over the 15-month follow-up period. The authors suggest that the lack of benefit in this study may be related to the already high level of care patients received as usual treatment and that a brief, 15-minute telephone-based intervention may not confer any incremental benefit in this case.(340)

The prior study that drove this recommendation was McKay et al. (2010).(341) McKay et al. (2010) also showed that continuing care can be effectively provided via telephone-based care.(341) Briefly, 252 patients who completed at least 3-weeks of a 3 – 4 month intensive outpatient treatment program (IOP) were randomized to (1) IOP only, (2) IOP plus up to thirty-six 5-10 minute phone calls that provided monitoring and feedback, or (3) IOP plus up to thirty-six 15 – 30 minute phone calls that included specific CBT counseling techniques linked to the results of the monitoring. Over the 18-month follow-up, the telephone condition that included counseling showed greater improvements in any alcohol use, any heavy alcohol use, days of alcohol use, and days of heavy alcohol use, relative to TAU. Treatment retention was also improved in this group. Longer phone calls that included counseling as compared to just brief telephone visits appeared to be most effective.

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation (339, 340) and considered the assessment of the evidence put forth in the 2015 VA/DoD SUD CPG.(341) The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including, small sample sizes, and lack of generalizability of the intervention. The benefits (i.e., increased access, especially in rural areas, for people with logistical challenges [distance to care, work/childcare concerns] and for the medically compromised compared to in-person appointments) outweighed the potential harms, of which none were identified. Patient values and preferences were similar, and the Work Group recognizes that telephone-based care continues to be more and more important for the treatment of SUD in the outpatient setting. Thus, the Work Group decided upon a *Weak for* recommendation.

Newer studies will need to be conducted in this area as telephone-based care has continued to evolve, as has patients' acceptability of this platform. In addition, with current conditions, telephone-based care continues to grow in popularity because of its ease of use and accessibility (with cellphone availability). Future research will need to be conducted to better understand how telephone-based care has continued to evolve as have patient preferences for this modality.

Recommendation

34. There is insufficient evidence to recommend for or against the use of telemedicine-delivered treatment for substance use disorders.
    (Neither for nor against | Reviewed, New-added)

Discussion

An RCT by Tarp et al. (2017) compared TAU for AUD treatment with the intervention group option of TAU augmented via videoconferencing.(342) It found fewer dropouts from those patients who received the intervention but was deemed very low quality due to small sample size (i.e., 71 adults with AUD), dropout rate, lack of direct outcomes of interest, and because the trial was insufficiently powered to draw conclusions.

While there was insufficient evidence to assess benefit for critical outcomes, there are no specific known harms. There are also potential benefits to telemedicine given barriers with transportation, rural areas that may make travel difficult or expensive, continuity of care for DoD patients who move every 2 – 3 years, and the potential for it to benefit medically compromised patients. Telemedicine may also add an additional way to address privacy concerns for some active duty Service Members. In addition, this may be a feasible option for patients who have scheduling conflicts due to work or childcare issues. Thus, telemedicine may increase access to care. During COVID-19, when this CPG was largely drafted, telemedicine increased out of necessity; this will likely lead to more post-COVID-19 acceptability by patients and more rapid adoption by providers and health systems.(343) As such, the Work Group anticipates additional research will continue to evolve in this area.

There are some factors providers should consider, including that patients may not feel comfortable with telemedicine, and computer-based technology may require additional resources like a computer, tablet, or internet connection. Comfortability with telemedicine may increase over time, more technology-literate

and/or younger patient populations may be more receptive to this, and it may be more widely utilized in the era of COVID-19.

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation.(342) The Work Group's confidence in the quality of the evidence was very low. The body of evidence had severe limitations including small sample size and indirectness of the evidence. The benefits and harms were balanced because both were minimal. Patient values and preferences likely vary with age, access to technology, and comfort with technology. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

More research is needed on the effectiveness of telemedicine-delivered treatments for patients with SUD. There is a need for larger sample sizes, longer follow-up periods, and future studies in VA/DoD populations to assess if there are differences in the success of these programs based on the different types of SUD. In addition, studies must be adequately powered to see an effect from treatment. Finally, there is a need for testing additional modalities for delivering telemedicine in the future.

Recommendation

35. There is insufficient evidence to recommend for or against the use of computer-delivered behavioral treatments, either alone or in combination with usual care, for substance use disorders. **(Neither for nor against | Reviewed, New-added)**

Discussion

The computer-delivered behavioral treatments considered (e.g., computer-delivered forms of CBT or MET) here were distinct from therapy delivered by the therapist via telemedicine considered in Recommendation 34, distinct from technology-based interventions (e.g., automated text/voice messaging, smartphone apps) considered in Recommendations 31 and 32, and distinct from use of structured telephone-based care as an adjunct to care considered in Recommendation 33.

Computer-delivered behavioral treatments for SUD, either alone or in combination with usual care, had insufficient evidence to recommend either for or against. This recommendation does not consider computer-delivered interventions for heavy or hazardous drinking. Of the included literature, nine RCTs compared computer-delivered therapeutic interventions to in-person TAU for the treatment or monitoring of adults with SUD. The confidence in the quality of the evidence for the critical outcome of abstinence was very low in three RCTs that compared computer-delivered CBT4CBT (344-346) and two studies (347, 348) that compared other forms of computer-delivered CBT or CBT plus MET, to in-person TAU. Of note, one study mentioned in Recommendation 31 used app-delivered CRA (ReSET); although this study did not meet the inclusion criteria for this CPG's systematic evidence review, the FDA found the evidence sufficient to clear the ReSET application.

Three studies assessed varied computer-delivered approaches to substance use treatment, including monitoring and relapse prevention.(349-351) The findings of all but one study indicated no difference between the computer-delivered and in-person forms of therapy. None of these three studies were designed as non-inferiority studies (i.e., testing the hypothesis of no difference); therefore, the data do not allow a determination on equivalence.

The one study that did show a difference, Murphy et al. (2016), compared an internet version of the CRA with CM known as therapeutic education system (TES) to standard outpatient therapy for SUD.(350) The study found that patients who received TES experienced more days of abstinence and remained in treatment longer than those in TAU.

The strength of the evidence addressing these computer-delivered therapies was very low. These ratings are primarily due to limitations in the methodological quality and size of the RCTs. All studies had some degree of attrition, and some also did not report on the randomization process or blinding of outcome assessors. The strength of the evidence was further limited by very small sample sizes. The overall sample size in most of the studies was less than 50 patients per treatment arm.

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation.(344-351) The Work Group's confidence in the quality of the evidence was very low. The body of evidence had limitations in the methodological quality, the size of the included RCTs, and attrition rate. Benefits and harms/burden (e.g., the removal of a therapist) were balanced. Patient values and preferences somewhat vary. While computerized therapies may be welcomed by some patients in remote or resource-constrained settings or systems, for others, the additional time, impersonal nature, real or perceived technical issues, or "the replacement of therapist time" may impede engagement in computer-delivered treatments. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

More research is needed on the effectiveness of computer-delivered treatments for patients with SUD. There is a need for larger sample sizes, longer follow-up periods, and studies in VA/DoD populations. Finally, particularly as technology, artificial intelligence, and both provider and user sophistication continue to advance, there is a need for testing additional (or combinations of) technologically oriented/delivered modalities in the future.

X. Future Research Priorities

During the development of the 2021 VA/DoD SUD CPG, the Work Group identified topics needing additional research, including areas requiring stronger evidence to support current recommendations and research exploring new areas to guide future CPGs.

Pharmacotherapy not studied in the U.S.

- Research is needed on other agents already studied in other countries but not yet in the U.S., including comparative effectiveness of sustained-release oral morphine versus continuing methadone for patients who use opioids while on methadone maintenance, and comparative effectiveness of intravenous hydromorphone versus continuing methadone for patients who use opioids while on methadone maintenance

New psychotherapies, behavioral therapies, and mobile health interventions

- Research is needed on new and innovative psychotherapies specifically designed to address the needs of patients with opioid use disorder on MOUD

- Research to develop adaptive algorithms to add targeted behavioral therapies when patients are not doing well on MOUD
- Studies of mobile health interventions that could serve to connect patients on MOUD with treatment providers between clinic visits and enable home drug testing with oral fluids (see Technology-based and technology-supported interventions below)

Pharmacotherapy for stimulant use disorder

- Research is needed on effective pharmacotherapies (more studies needed on specific agents) versus placebo for stimulant use disorder

Treatment for cannabis use disorder

- Research is needed on pharmacotherapies versus placebos for the treatment of cannabis use disorder
- Research is needed on non-pharmacologic treatments for cannabis use disorder

Contingency management

- Research is needed to further explore the effectiveness and implementation of CM for cannabis use disorder
- Research is needed to explore the use of CM to reduce opioid use and improve treatment retention in MOUD

Adjunctive medications for benzodiazepine withdrawal and treatment of benzodiazepine use disorder

- Larger RCTs with reasonably long (e.g., at least one year) follow-up periods are needed to evaluate medications adjunctive to benzodiazepines for benzodiazepine withdrawal management
- Research is needed on treatments that can help prevent relapse of benzodiazepine use disorder post withdrawal treatment

Opioid withdrawal strategies

- Because there are individuals who cannot be maintained on OAT due to work requirements or strong preference, research is needed on ways to withdraw patients from opioids more safely, comfortably, and quickly to facilitate the transition from opioids to injectable naltrexone

Mutual help groups

- Research is needed on the implementation of different interventions to encourage participation in mutual help groups
- Research is needed on ways to standardize and improve access to mutual help groups, including online and virtual formats

Screening for drug use disorders to facilitate enrollment in treatment

- Additional, well-designed studies, including RCTs, are needed to evaluate screening for drug use disorders in primary care and screening's effect on enrollment in treatment and other outcomes

Telehealth treatment

- Well-designed RCTs are needed to compare SUD treatment delivered in person versus SUD treatment delivered via telehealth

Technology-based and technology-supported interventions

- Research is needed to study technology-based interventions for drug use disorders (non-alcohol SUDs), app-based SUD treatment delivery, synchronous (i.e., non-automated) texting support with healthcare providers, as well as technology-supported interventions combined with in-person care or telemedicine. Additional research should also aim to generate step-based algorithms to personalize treatment and identify patients in need of additional (e.g., in-person) care.

Mindfulness-based therapies

- Research is needed on which patients (different substances of misuse, different treatment settings, different patient characteristics) are most likely to benefit from mindfulness-based approaches
- There is also a need for larger, multi-site randomized trials to determine the efficacy and comparative effectiveness of mindfulness-based therapies

Substance use disorder treatment in the older population

- With an aging Veteran population, there is an increasing number of older Veterans with alcohol and drug use disorders. Research is needed as there has been limited research to date looking into the most effective SUD treatment management strategies for this older population.

Substance use disorder treatment implementation in non-specialty settings

- Research is needed to investigate multidisciplinary models of SUD care within primary care, mental health, and other non-specialty care settings, and effective implementation strategies to improve utilization of medication treatment for AUD and OUD in these settings

Racial and ethnic disparities in substance use disorder treatment

- Research is needed to identify and address racial/ethnic and other disparities (e.g., gender, environmental, social) in SUD treatment access and outcomes

Care coordination and transitions

- Research is needed to improve effective coordination between VA and DoD care and community care settings for addiction treatment
- Research is needed to improve addiction treatment coordination for Veterans transitioning from DoD to VA care

Stigma reduction

- Research is needed to reduce stigma of addiction and stigma of addiction treatment

Appendix A: Guideline Development Methodology

A. Developing Key Questions to Guide the Systematic Evidence Review

To guide this CPG's systematic evidence review, the Work Group drafted 12 KQs on clinical topics of the highest priority for the VA and DoD populations. The KQs followed the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework, as established by AHRQ (see Table A-1).

Table A-1. PICOTS (352)

PICOTS Element	Description
Population or Patients	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.
Intervention or Exposure	Treatment (e.g., drug, surgery, lifestyle changes), approach (e.g., doses, frequency, methods of administering treatments), or diagnostic /screening test used with the patient or population.
Comparator	Treatment(s) (e.g., placebo, different drugs) or approach(es) (e.g., different dose, different frequency, standard of care) that are being compared with the intervention or exposure of interest described above.
Outcomes	Results of interest (e.g., mortality, morbidity, quality of life, complications). Outcomes can include short, intermediate, and long-term outcomes.
Timing, if applicable	Duration or follow-up of interest for the particular patient intervention and outcome to occur (or not occur).
Setting, if applicable	Setting or context of interest. Setting can be a location (e.g., primary, specialty, inpatient care) or type of practice.

Abbreviation: PICOTS: population, intervention, comparison, outcome, timing, and setting

Due to resource constraints, all KQs of interest to the Work Group could not be included in the systematic evidence review. Thus, the Work Group selected the 12 highest priority KQs for inclusion in the systematic evidence review (see Table A-2).

Using the GRADE approach, the Work Group rated each outcome on a 1 – 9 scale (7 – 9, critical for decision making; 4 – 6, important, but not critical, for decision making; and 1 – 3, of limited importance for decision making). Critical and important outcomes were included in the evidence review (see Outcomes); however, only critical outcomes were used to determine the overall quality of evidence (see Grading Recommendations).

a. Population(s)

- Key Question 1: Including adults with a DSM diagnosis of OUD
- Key Question 2: Including adults with a DSM diagnosis of OUD who are on pharmacotherapy
- Key Question 3: Including adults with a DSM diagnosis of stimulant/(meth) amphetamine or cocaine use disorder
- Key Questions 4, 5: Including adults with a DSM diagnosis of cannabis use disorder
- Key Question 6: Including adults with moderate to severe risk of benzodiazepine withdrawal
- Key Question 7: Including adults with moderate to severe risk of opioid withdrawal

- Key Question 8: Including adults with a DSM diagnosis of an SUD (alcohol, cannabis, opioids, stimulants [cocaine/amphetamines], poly-drug use if it includes one of these four categories)
- Key Question 9: Including adults (universal screening)
- Key Questions 10 – 12: Including adults with a DSM diagnosis of SUD

b. Interventions

- Key Question 1 – Pharmacotherapy:
  - Opioid agonists:
    - Full opioid agonist: Methadone
    - Partial opioid agonist: Buprenorphine, Implantable buprenorphine, Monthly injectable buprenorphine
    - Partial opioid agonist/antagonist: Buprenorphine/naloxone
  - Opioid antagonists: Injectable naltrexone, Oral naltrexone
- Key Question 2 – Pharmacotherapy plus one of the following behavioral therapies: Addiction-focused couples therapy, CBT for addiction, CRA, CM therapy for addiction, MET for addiction, MI for SUDs, Individual social skills training focused on addiction, Family Psychoeducation (FPE) focused on addiction, TSF
- Key Question 3 – Pharmacotherapies:
  - Agonist replacement therapy (e.g., mixed amphetamine salts, methylphenidate, dextroamphetamine)
  - Skeletal muscle relaxants: Baclofen
  - Antidepressant: Bupropion
  - Tricyclic antidepressants: Desipramine
  - Alcohol antagonist: Disulfiram
  - Alpha-blocker: Doxazosin
  - Acetylcholinesterase inhibitor: Galantamine
  - Antidepressant (NaSSA): Mirtazapine
  - Wakefulness promoting agent: Modafinil
  - Opiate antagonist: Naltrexone
  - Muscle relaxant/anticonvulsant: Topiramate
  - Anticonvulsant: Vigabatrin
- Key Question 4 – Pharmacotherapy:
  - SNRI: Atomoxetine
  - Skeletal muscle relaxant: Baclofen
  - Antidepressant: Bupropion, Nefazodone

- Anxiolytics: Buspirone
- Alpha-agonist hypotensive: Clonidine
- Anti-epileptics: Divalproex
- Cannabinoids: Dronabinol, Nabilone
- COMT inhibitors: Entacapone
- SSRI: Fluoxetine
- Anticonvulsant: Gabapentin
- Antipsychotic: Lithium
- Alpha-adrenergic agonist: Lofexidine
- Antidepressant (NaSSA): Mirtazapine
- Mucolytic agent: N-acetylcysteine

- Key Question 5
  - Addiction-focused couples therapy
  - CBT for addiction
  - CRA
  - CM therapy for addiction
  - MET for addiction
  - MI for SUD
  - Individual social skills training focused on addiction
  - FPE focused on addiction
  - TSF
- Key Question 6: Pharmacotherapies
  - Anxiolytic: Alpidem, Buspirone, Captodiame
  - Beta-blockers: Acebutolol, Atenolol, Betaxolol, Bisoprolol, Metoprolol succinate, Metoprolol tartrate, Nadolol, Nebivolol, Penbutalol, Pindolol, Propanolol, Timolol
  - Anti-epileptics: Divalproex sodium/Valproate sodium/Valproic acid
  - Benzodiazepine antagonist: Flumazenil
  - SSRI: Fluoxetine, Paroxetine
  - Anticonvulsant: Gabapentin, Carbamazepine, Pregabalin
  - Longer-acting benzodiazepines (i.e., diazepam, clonazepam)
  - 50HT3 antagonist: Ondansetron
  - Antidepressant: Sertraline
  - Tricyclic antidepressants

- Key Question 7: Pharmacotherapies
    - Partial opioid agonist: Buprenorphine
    - Alpha-agonist hypotensive: Clonidine
    - Anticonvulsant: Gabapentin
    - Agonist: Guanfacine
    - Antipsychotics: Haloperidol
    - Alpha-adrenergic agonist: Lofexidine (new, approved for use for up to 14 days)
    - Full opioid agonist: Methadone
    - Antidepressent (NaSSA): Mirtazapine
    - Skeletal muscle relaxants: Tizanidine
    - Opiate (narcotic) analgesics: Tramadol
    - SNRI: Venlafaxine
- Key Questions 8 – 12: Step facilitation and other branded strategies: Making AA easier, TSF, Enhanced Referral, NS, STAGE-12
- Key Question 9: Screening instruments delivered in-person, virtually, or through telephone
    - ASSIST: Alcohol, Smoking, and Substance Involved Screening Test
    - SURP-P: Substance Use Risk Profile-Pregnancy Scale
    - 4P's
    - NIDA Quick Screen
    - CRAFFT
    - DAST-10: Drug Abuse Screening Test
    - TAPS: Tobacco, Alcohol, Prescription medication, and other Substance use tool
    - WIDUS: Wayne Indirect Drug Use Screener
- Key Question 10: Any telehealth or virtual health technology (audio+/-video) delivery via computer, tablet, or smartphone, or telephone
- Key Question 11: Usual care and technology-supported management such as apps (mobile, web-based, call and text helplines)
- Key Question 12: Addition-focused mindfulness-based therapies: ACT, MBRP

c. Comparators

- Key Question 1: Another listed pharmacotherapy, Different intensity (e.g., low vs. higher) or duration (e.g., time-limited vs. indefinite) of treatment
- Key Question 2: Pharmacotherapy alone
- Key Questions 3, 4: Another listed medication

- Key Question 5: Different addiction-focused psychotherapies or psychosocial interventions
- Key Question 6: Another listed medication, Taper without benzodiazepine substitution
- Key Question 7: Other listed medications as active controls (not to include placebo-controlled studies of lofexidine or other agents)
- Key Question 8: No use of a specific strategy or use of a different strategy
- Key Question 9: No screening, usual care, or one screening strategy versus another
- Key Question 10: Usual care setting (in-person care)
- Key Question 11: Usual care alone
- Key Question 12: Standard of care or traditional/usual addiction-focused therapies

d. Outcomes

- Key Questions 1, 2:
    - Critical outcomes: Opioid consumption/abstinence/frequency of use, Retention/duration in treatment, QoL, Mortality (includes death by suicide), Overdoses (includes intentional)
    - Important outcomes: Relapse/Time to relapse, Hospitalization or readmission/ER use
- Key Question 3:
    - Critical outcomes: Stimulant consumption/abstinence/frequency of use, Retention/duration in treatment, QoL, Mortality (includes death by suicide), Overdoses (includes intentional)
    - Important outcomes: Craving, Relapse/Time to relapse
- Key Questions 4, 5:
    - Critical outcomes: Cannabis consumption/abstinence/frequency of use, Relapse/Time to relapse, Retention/duration in treatment, QoL, Overdoses (includes intentional)
    - Important outcomes: Consumption outcomes: Craving, Mortality (includes death by suicide)
- Key Question 6:
    - Critical outcomes: Benzodiazepine/Z-drug consumption, Relapse/Time to relapse, Withdrawal symptoms, Mortality (includes death by suicide), Overdoses (includes intentional), Seizures
    - Important outcomes: Hospitalization or readmission/ER use
- Key Question 7:
    - Critical outcomes: Opioid consumption/frequency of use, Withdrawal symptoms, Retention/duration in treatment, Mortality (includes death by suicide), Suicide ideation/attempt
    - Important outcomes: Adherence with treatment, Overdoses (includes intentional)

- Key Question 8:
  - Critical outcomes: Consumption/abstinence/frequency of use, Duration of involvement in mutual help programs, QoL
  - Important outcomes: Enrollment in mutual help programs, Minimal length of stay in mutual health programs/minimum number of mutual help visits
- Key Question 9:
  - Critical outcomes: Linkage to care as appropriate, Further assessment, Enrollment in care
  - Important outcomes: QoL
- Key Questions 10, 11:
  - Critical outcomes: Substance use consumption/abstinence/frequency of use, Retention/duration in treatment, QoL, Mortality (includes death by suicide), Hospitalization or readmission/ER use
  - Important outcomes: Relapse/Time to relapse, Adherence with treatment
- Key Question 12
  - Critical outcomes: Substance use consumption/abstinence/frequency of use, Adherence outcomes: Retention/duration in treatment, QoL, Mortality (includes death by suicide), Hospitalization or readmission/ER use
  - Important outcomes: Relapse/Time to relapse, Suicidal ideation/attempt

e. Timing

- Key Questions 1, 3, 4: Minimum follow-up four weeks
- Key Questions 2, 5, 12: Minimum follow up 12 weeks
- Key Questions 6 – 9: Any
- Key Questions 10, 11: Minimum follow-up of four weeks or 12 weeks depending on treatment delivered through telehealth, Any follow-up for monitoring

f. Setting

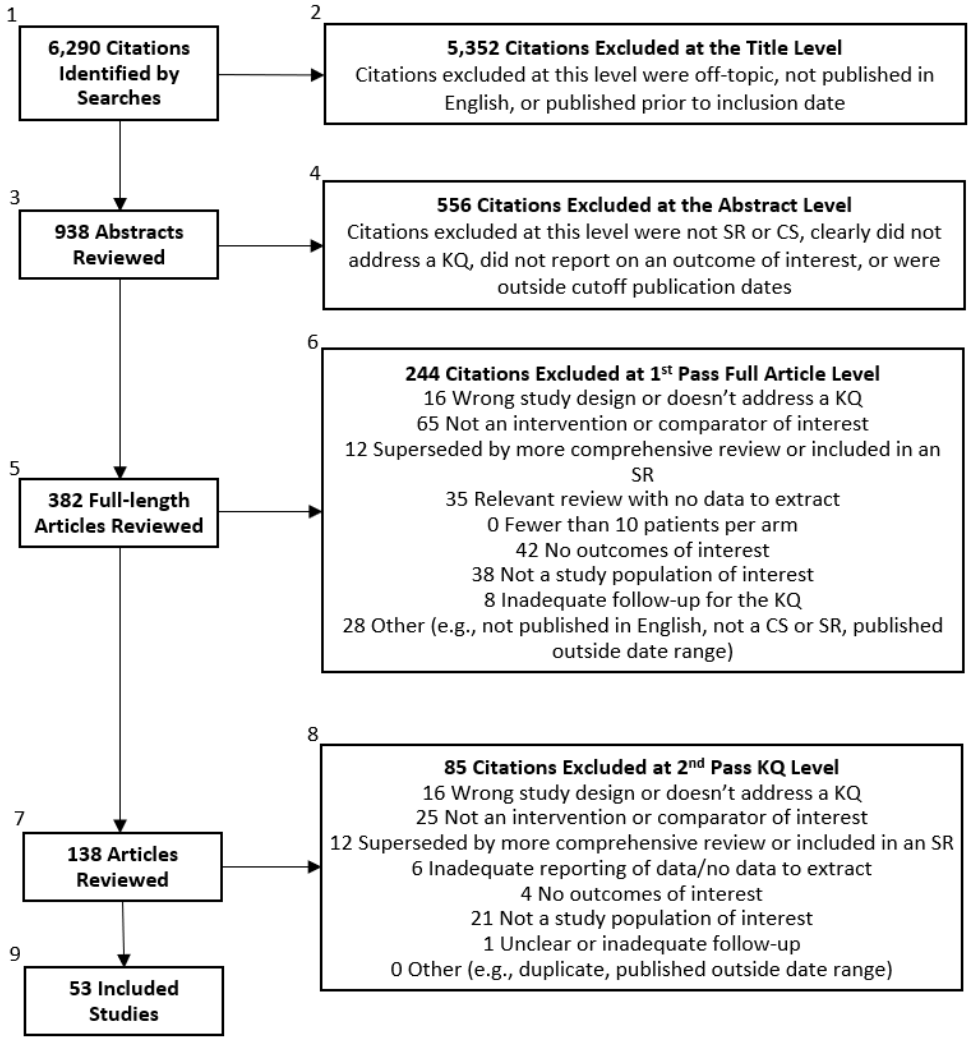
- Key Questions 1 – 12: Primary care or specialty care

B. Conducting the Systematic Review

Based on the Work Group's decisions regarding the CPG's scope, KQs, and PICOTS statements, the Lewin Team produced a systematic evidence review protocol before conducting the review. The protocol detailed the KQs, PICOTS criteria, methodology to be used during the systematic evidence review, and the inclusion and exclusion criteria to be applied to each potential study, including study type and sample size. The Work Group reviewed and approved the protocol.

Figure A-1 below outlines the systematic evidence review's screening process (see also the General Criteria for Inclusion in Systematic Review and Key Question Specific Criteria). In addition, Table A-2 indicates the number of studies that addressed each of the questions.

Figure A-1. Study Flow Diagram



Abbreviations: CS: clinical study; KQ: key question; SR: systematic review

Alternative Text Description of Study Flow Diagram

Figure A-1. Study Flow Diagram is a flow chart with nine labeled boxes linked by arrows that describe the literature review inclusion/exclusion process. Arrows point down to boxes that describe the next literature review step and arrows point right to boxes that describe the excluded citations at each step (including the reasons for exclusion and the numbers of excluded citations).

1. Box 1: 6,290 citations identified by searches
    a. Right to Box 2: 5,352 citations excluded at the title level
        i. Citations excluded at this level were off-topic, not published in English, OR published prior to inclusion date
    b. Down to Box 3
2. Box 3: 938 abstracts reviewed
    a. Right to Box 4: 556 citations excluded at the abstract level
        i. Citations excluded at this level were not an SR or CS, clearly did not address a KQ, did not report on or an outcome of interest, OR were outside cutoff publication dates
    b. Down to Box 5
3. Box 5: 382 full-length articles reviewed
    a. Right to Box 6: 244 citations excluded at 1st pass full article level
        i. 16 citations excluded at this level had the wrong study design or did not address a KQ
        ii. 65 citations excluded at this level did not have an intervention or comparator of interest
        iii. 12 citations excluded at this level were superseded by more comprehensive review or included in an SR
        iv. 35 citations excluded at this level had relevant reviews with no data to extract
        v. No citations excluded at this level had fewer than 10 patients per arm
        vi. 42 citations excluded at this level had no outcomes of interest
        vii. 38 citations excluded at this level did not study a population of interest
        viii. 8 citations excluded at this level had inadequate follow-up for the KQ
        ix. 28 citations excluded at this level were excluded for another reason (e.g., duplicate, published outside date range)
    b. Down to Box 7

4. Box 7: 138 articles reviewed
    a. Right to Box 8: 85 citations excluded at 2nd pass KQ level
        i. 16 citations excluded at this level had the wrong study design or did not address a KQ
        ii. 25 citations excluded at this level did not have an intervention or comparator of interest
        iii. 12 citations excluded at this level were superseded by more comprehensive review or included in an SR
        iv. 6 citations excluded at this level had inadequate reporting of data OR no data to extract
        v. 4 citations excluded at this level had no outcomes of interest
        vi. 21 citations excluded at this level did not study a population of interest
        vii. 1 citation excluded at this level had unclear or inadequate follow-up
        viii. No citations excluded at this level were excluded for another reason (e.g., duplicate, published outside date range)
    b. Down to Box 9
5. Box 9: 53 Included Studies

Table A-2. Evidence Base for KQs

KQ Number	KQ	Number and Study Type
1	In adults with a DSM diagnosis of opioid use disorder, what is the comparative effectiveness of pharmacotherapy, including different intensity and duration of treatment, for improving consumption outcomes, adherence outcomes, and adverse events?	2 SRs 6 RCTs
2	In adults with a DSM diagnosis of opioid use disorder, what is the comparative effectiveness of pharmacotherapy with or without addiction-focused psychotherapies or psychosocial interventions for improving consumption outcomes, adherence outcomes, and adverse events?	1 SR 4 RCTs
3	In adults with a DSM diagnosis of stimulant 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
4	In adults with a DSM diagnosis of cannabis use disorder, what is the comparative effectiveness of pharmacotherapy for improving consumption outcomes, adherence outcomes, and adverse events?	No evidence
5	In adults with a DSM diagnosis of cannabis use disorder, what is the comparative effectiveness of addiction-focused psychotherapies or psychosocial interventions for improving consumption outcomes, adherence outcomes, and adverse events?	1 SR 3 RCTs
6	For patients with moderate to severe risk of benzodiazepine withdrawal, what is the comparative effectiveness of pharmacotherapy for benzodiazepine withdrawal management?	1 SR
7	For patients with moderate to severe risk of opioid withdrawal, what is the comparative effectiveness of pharmacotherapy for stabilization? Does comparative effectiveness vary based on dosing and time course used with the pharmacotherapies?	2 SRs 3 RCTs
8	In adults with a DSM diagnosis of a substance use disorder, what is the comparative effectiveness of strategies used for promoting active involvement in available mutual help programs for improving recovery and engagement outcomes?	1 SR 2 RCTs
9	In adults, does screening for substance use disorder result in increased enrollment in treatment and improved health outcomes?	1 observational pre-post study
10	In adult patients with a DSM diagnosis of a substance use disorder, what is the effectiveness of telehealth and virtual health modalities compared to a usual care setting?	10 RCTs
11	In adult patients with a DSM diagnosis of a substance use disorder, what is the effectiveness of technology-based interventions as an adjunct to usual care in improving outcomes?	6 RCTs
12	In adults with a DSM diagnosis of substance use disorder, what is the effectiveness of addiction-focused mindfulness-based therapies (e.g., ACT, mindfulness-based relapse prevention) for improving recovery outcomes?	1 SR 8 RCTs
	Total Evidence Base	**54 studies***

*One study was used in more than one KQ

Abbreviations: ACT: acceptance and commitment therapy; DSM: Diagnostic and Statistical Manual; KQ: key question; RCT: randomized controlled trial; SR: systematic review

a. General Criteria for Inclusion in Systematic Evidence Review

- Randomized controlled trials or SRs published on or after January 1, 2015, to June 30, 2020. If multiple SRs addressed a KQ, we selected the most recent and/or comprehensive review. Systematic reviews were supplemented with RCTs published after the SR.
- 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.
- Systematic reviews must have searched MEDLINE or EMBASE for eligible publications, performed a risk of bias assessment of included studies, and assessed the quality of evidence using a recognizable rating system, such as GRADE or something compatible (e.g., the Strength of Evidence grading used by the Evidence-based Practice Centers of AHRQ). If an existing review did not assess the overall quality of the evidence, evidence from the review must be reported in a manner that allows us to judge the overall risk of bias, consistency, directness, and precision of evidence. We did not use an existing review as evidence if we were not able to assess the overall quality of the evidence in the review.
- Study must have enrolled at least 20 patients (10 per study group); small sample size is associated with increased risk of bias, and we downgrade small studies in the GRADE domain of precision: one downgrade for imprecision of a single study with <200 patients per study arm and 2 downgrades for imprecision for <50 total patients.
    - Newer Cochrane reviews already take into account small sample size in their estimation of risk of bias. In these cases, where sample size has already contributed to the assessment of the evidence, we do not downgrade those data a second time.
- Study must have enrolled at least 85% of patients who meet the study population criteria: adults aged 18 years or older with a diagnosed SUD. For studies examining mixed patient populations, studies must have enrolled at least 85% of patients with the relevant condition.
- Studies that specifically focus on adults with nicotine use disorder only or studies of adults who are incarcerated or undergoing mandated classes related to DWI/DUI without a diagnosed SUD were excluded.
- Study must have reported on at least one outcome of interest.

b. Key Question Specific Criteria for Inclusion in Systematic Evidence Review

- For all KQs, except KQ 9, studies must be a prospective, RCT with an independent control group. Crossover trials were not included unless they report data for the first phase of the study separately.
- KQ 9 included non-randomized study designs that assessed a valid substance use screening tool and reported on patient enrollment in treatment, linkage to care, or further assessment. KQ 9 did not include assessment of alcohol screening instruments as these were covered in the 2015 VA/DoD SUD CPG.

c. Literature Search Strategy

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

Table A-3. Bibliographic Database Information

Name	Date Limits	Platform/Provider
Embase (Excerpta Medica) and MEDLINE	January 1, 2015, to June 30, 2020	Elsevier
PsycINFO	January 1, 2015, to June 30, 2020	Ovid
PubMed (In-process and Publisher records)	January 1, 2015, to June 30, 2020	NLM
Agency for Healthcare Research and Quality (AHRQ)	January 1, 2015, to June 30, 2020	AHRQ
U.S. Department of Veterans Affairs (VA) Evidence Synthesis Program	January 1, 2015, to June 30, 2020	VA

C. Developing Evidence-based Recommendations

In consultation with the VA Office of Quality and Patient Safety and the Clinical Quality Improvement Program, DHA, the Lewin Team convened a four-day virtual recommendation development meeting on October 20 – 23, 2020, to develop this CPG's evidence-based recommendations. Two weeks before the meeting, the Lewin Team finalized the systematic evidence review and distributed the report to the Work Group; findings were also presented during the first day of the recommendation development meeting.

Led by the Champions, the Work Group interpreted the systematic evidence review's findings and developed this CPG's recommendations. Where appropriate, the Work Group carried forward and modified recommendations from the 2015 VA/DoD SUD CPG as necessary (see 2015 Recommendation Categorization Table). The Work Group also developed new recommendations not included in the 2015 VA/DoD SUD CPG based on the 2020 evidence review.

As the Work Group drafted recommendations, they also rated each recommendation based on a modified GRADE and USPSTF methodology. Recommendations were rated by assessing the quality of the overall evidence base, the associated benefits and harms, patient values and preferences, and other implications.

a. Grading Recommendations

Per GRADE, each recommendation's strength and direction is determined by the following four domains:(87)

1. Confidence in the Quality of the Evidence

Confidence in the quality of the evidence reflects the quality of the evidence base supporting a recommendation. The options for this domain include: *High*, *Moderate*, *Low*, or *Very low*. This is a direct reflection of the GRADE ratings for each relevant critical outcome in the evidence review (see Outcomes). Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(89, 90)

The recommendation strength generally aligns with the confidence in the quality of evidence. For example, *Strong* recommendations are typically supported by *High* or *Moderate* quality evidence. However, GRADE permits *Low* or *Very low* quality evidence to support a *Strong* recommendation in certain instances (e.g., life-threatening situation).(87)

2. Balance of Desirable and Undesirable Outcomes

The balance of desirable and undesirable outcomes (i.e., benefits and harms) refers to the relative magnitudes or tradeoffs of anticipated benefits (e.g., increased longevity, reduced morbidity, improved quality of life, decreased resource use) and harms (e.g., decreased longevity, increased complications, impaired quality of life). The options for this domain include: *benefits outweigh harms/burden*, *benefits slightly outweigh harms/burden*, *benefits and harms/burdens are balanced*, *harms/burdens slightly outweigh benefits*, and *harms/burdens outweigh benefits*. This domain assumes most clinicians will offer patients an intervention if its advantages exceed the harms. The Work Group's understanding of the benefits and harms associated with the recommendation influenced the recommendation's strength and direction.

3. Patient Values and Preferences

Patient values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life as they may apply to the intervention's potential benefits, harms, costs, limitations, and inconvenience. The options for this domain include: *similar values*, *some variation*, or *large variation*. For instance, there may be *some variation* in patient values and preferences for a recommendation on the use of acupuncture, as some patients may dislike needles. When patient values seem homogeneous, this domain may increase the recommendation's strength. Alternatively, when patient values seem heterogeneous, this domain may decrease a recommendation's strength. As part of this domain, the Work Group considered the findings from the patient focus group carried out as part of this CPG update (see Appendix F).

4. Other Implications

Other implications encompass the potential consequences or other impacts that might affect the strength or direction of the recommendation. The options for this domain include, e.g.: resource use, equity, acceptability, feasibility, and subgroup considerations. The following are example implications related to equity and subgroup considerations, respectively: some of the indicated population may be geographically remote from an intervention (e.g., complex radiological equipment); a drug may be contraindicated in a subgroup of patients.

Table A-4. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgment
Confidence in the quality of the evidence	Among the designated critical outcomes, what is the lowest quality of relevant evidence? How likely is further research to change the confidence in the estimate of effect?	High Moderate Low Very low
Balance of desirable and undesirable outcomes	What is the magnitude of the anticipated desirable outcomes? What is the magnitude of the anticipated undesirable outcomes? Given the best estimate of typical values and preferences, are you confident that benefits outweigh harms/burdens or vice versa?	Benefits outweigh harms/burdens Benefits slightly outweigh harm/burden Benefits and harms/burdens are balanced Harms/burdens slightly outweigh benefits Harms/burdens outweigh benefits
Patient values and preferences	What are the patients' values and preferences? Are values and preferences similar across the target population? Are you confident about typical values and preferences?	Similar values Some variation Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	What are the costs per resource unit? Is this intervention generally available? What is the variability in resource requirements across the target population and settings? Are the resources worth the expected net benefit from the recommendation? Is this intervention and its effects worth withdrawing or not allocating resources from other interventions?	Various considerations

b. Recommendation Categorization

A summary of the recommendation categories and definitions is available in Table 3.

1. Categorizing Recommendations with an Updated Review of the Evidence

Reviewed refers to recommendations on topics included in this CPG's systematic evidence review. *Reviewed*, *New-added* recommendations are original, new recommendations (i.e., not included in the previous CPG). These recommendations are based entirely on evidence included in the current CPG's systematic evidence review.

Reviewed, *New-replaced* recommendations were in the previous CPG but revised based on the updated evidence review. These recommendations may have clinically relevant edits. *Reviewed*, *Not changed* recommendations were carried forward from the previous CPG unchanged. *Reviewed*, *Amended* recommendations were carried forward from the previous CPG with a nominal change. This allowed for the recommendation language to reflect GRADE approach and any other not clinically meaningful edits deemed necessary. These recommendations can be based on a combination of evidence included in the current CPG's systematic evidence review and the evidence base that supported the recommendation in the previous CPG.

Reviewed, *Deleted* refers to recommendations from the previous CPG that were deleted after a review of the evidence. This may occur if the evidence supporting the recommendation is outdated (e.g., there is no

longer a basis to recommend use of an intervention and/or new evidence suggests a shift in care), rendering the recommendation obsolete.

2. 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 CPG without an updated review of the evidence. Given time and resource constraints, the systematic evidence review carried out for this CPG update could not cover all available evidence on SUD; therefore, its KQs focused on new or updated research or areas not covered in the previous CPG.

For areas in which the relevant evidence was not changed and for which recommendations made in the previous CPG were still relevant, recommendations could have been carried forward to the updated CPG without an updated review of the evidence. The evidence supporting these recommendations was thus also carried forward from the previous 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 were carried forward from the previous CPG unchanged. *Not reviewed*, *Amended* recommendations were carried forward from the previous CPG with a nominal change. *Not reviewed*, *Deleted* recommendations were determined by the Work Group to not be relevant. A recommendation may not be relevant if it, for example, pertained to a topic (e.g., population, care setting, treatment) outside of the updated CPG's scope or if it was determined to be common practice.

The recommendation categories for the current CPG are noted in the Recommendations. The recommendation categories from the 2015 VA/DoD SUD CPG are noted in Appendix E.

D. Drafting and Finalizing the Guideline

The Work Group wrote, reviewed, and edited three drafts of the CPG using an iterative review process to solicit feedback on and make revisions to the CPG. The first and second drafts were posted online for 20 and 14 business days, respectively, for the Work Group to provide feedback. Draft 3 was made available for a 14-day peer review and comment (see External Peer Review). The Work Group reviewed all feedback submitted during each review period and made appropriate revisions to the CPG. Following the Draft 3 review and comment period, the Work Group reviewed external feedback and created a final draft of the CPG. The Champions then presented the CPG to the EBPWG for approval. The Work Group considered the EBPWG's feedback and revised the CPG as appropriate to create the final version. To accompany the CPG, the Work Group produced toolkit products, including a provider summary, pocket card, and patient summary. The EBPWG approved the final CPG and toolkit products in August 2021.

Appendix B: Pharmacotherapy

Table B-1. Pharmacotherapy for Alcohol Use Disorder[a,b]

Topic Area	Naltrexone Oral	Naltrexone Injectable	Acamprosate	Disulfiram	Topiramate	Gabapentin
Indications	AUD (DSM diagnosis) with: • Not required, but recommended for improved response: At least 2 – 4 days of pretreatment abstinence • Not required, but recommended: Initial engagement in addiction-focused medical management and/or other recommended psychosocial intervention	AUD (DSM diagnosis) with: • Not required, but recommended for improved response: At least 2 – 4 days of pretreatment abstinence • Willingness to receive monthly injections • Not required, but recommended: Initial engagement in addiction-focused medical management and/or other recommended psychosocial intervention	AUD (DSM diagnosis) with: • Not required, but recommended: Initial engagement in addiction-focused medical management and/or other recommended psychosocial intervention	AUD (DSM diagnosis) with: • Abstinence >12 hours and BAL=0 • Capacity to appreciate risks and benefits and to consent to treatment • Appropriate if goal is total alcohol abstinence • Not required, but recommended: Initial engagement in addiction-focused medical management and/or other recommended psychosocial intervention • Note: More effective with monitored administration (e.g., in clinic, with spouse, with probation officer)	AUD (DSM diagnosis) (off label) with: • Pretreatment abstinence not required but may improve response • Not required, but recommended: Initial engagement in addiction-focused medical management and/or other recommended psychosocial intervention	AUD (DSM diagnosis) (off label) with: • Not required, but recommended for improved response: At least 2 – 4 days of pretreatment abstinence • Not required, but recommended: Initial engagement in addiction-focused medical management and/or other recommended psychosocial intervention

[a] While this table provides evidence-based suggestions for dosage and administration of medications for OUD and AUD, some strategies (e.g., microdosing) are not explained here. Providers should use clinical judgment and engage in shared decision making to determine appropriate initiation, titration, and dosage strategy for each patient.

[b] Topiramate and gabapentin are not FDA labeled for treatment of AUD.

Topic Area	Naltrexone Oral	Naltrexone Injectable	Acamprosate	Disulfiram	Topiramate	Gabapentin
Contraindications	• Receiving opioid agonists • Physiologic opioid dependence with use within past 7 – 10 days (up to 14 days with use of buprenorphine or methadone) • Acute opioid withdrawal • Failed naloxone challenge test[c] • Positive urine opioid screen • Acute hepatitis or severe hepatic impairment • Hypersensitivity	• Receiving opioid agonists • Physiologic opioid dependence with use within past 7 – 10 days (up to 14 days with use of buprenorphine or methadone) • Acute opioid withdrawal • Failed naloxone challenge test • Positive urine opioid screen • Acute hepatitis or severe hepatic impairment • Hypersensitivity • Inadequate muscle mass	• Hypersensitivity • Severe renal insufficiency (CrCl ≤30 mL/min)	• Severe myocardial disease or coronary occlusion • Severe hepatic dysfunction (i.e., transaminase levels >3 times upper limit of normal or abnormal bilirubin) • Psychosis • Metronidazole, paraldehyde, alcohol, or alcohol-containing preparations • Hypersensitivity to disulfiram or other thiuram derivatives	• No contraindications in manufacturer's labeling. Alcohol should be avoided within 6 hours prior and 6 hours after topiramate XR administration.	• Hypersensitivity

[c] For more information on naloxone challenge testing, please see: https://www.ncbi.nlm.nih.gov/books/NBK535266/box/p3.b36/?report=objectonly

Topic Area	Naltrexone Oral	Naltrexone Injectable	Acamprosate	Disulfiram	Topiramate	Gabapentin
Warnings/Precautions	• Hepatotoxicity • Caution in patients with moderate-severe renal impairment • Vulnerability to opioid overdose on discontinuation • Diminished effects of opioid-containing medications • Insufficient evidence in pregnancy; use only if potential benefit outweighs the potential risk to the fetus	• Hepatotoxicity • Caution in patients with moderate-severe renal impairment • Injection site reactions • Depression and suicidal thoughts • Vulnerability to opioid overdose on discontinuation • Diminished effects of opioid-containing medications • Insufficient evidence in pregnancy; use only if potential benefit outweighs the potential risk to the fetus • Use intramuscular injections with caution in patients with thrombocytopenia or coagulation disorders	• Monitor for emergence of depression or suicidality • Reduce dose in patients with renal insufficiency (CrCl 30 – 50 mL/min) • Teratogenic in rats and rabbits • Insufficient evidence in pregnancy; use only if potential benefits outweighs the potential risk to fetus	• Alcohol-disulfiram reaction; patients must be vigilant to avoid alcohol in all forms (e.g., mouthwash, OTC medications) • Severe renal or hepatic impairment • Cerebrovascular disease or cerebral damage • Nephritis • Epilepsy • Hypothyroidism • Diabetes • Safety in pregnancy has not been established, use only when benefits outweigh the possible risks	• Do not abruptly discontinue; taper dosage gradually • Cognitive dysfunction, psychiatric disturbances, and sedation may occur • Acute myopia and secondary angle closure glaucoma • Oligohydrosis and hyperthermia • Metabolic acidosis • Increased risk of suicidal ideation with antiepileptic agents, including topiramate • Use during pregnancy can cause cleft lip and/or palate	• Do not abruptly discontinue; taper dosage gradually • May cause CNS depression including somnolence/ dizziness • Anaphylaxis and angioedema • Increased risk of suicidal ideation with antiepileptic agents, including gabapentin • Use during pregnancy may result in higher risk of preterm birth, NICU admission, and SGA

Topic Area	Naltrexone Oral	Naltrexone Injectable	Acamprosate	Disulfiram	Topiramate	Gabapentin
Baseline Evaluation	• Liver transaminase levels • Urine beta-HCG for females • Urine drug screen to confirm no opioid use	• Liver transaminase levels • Ensure patient has adequate muscle mass for injection • Urine beta-HCG for females • Urine drug screen to confirm no opioid use	• CrCl (estimated or measured) • Urine beta-HCG for females	• Liver transaminase levels • Complete blood count and serum chemistries • 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 • Serum bicarbonate • Urine beta-HCG for females	• CrCl (estimated or measured) • Urine beta-HCG for females
Dosage and Administration	• 50 mg orally once daily	• 380 mg every four weeks or monthly as a gluteal injection	• 666 mg orally three times daily	• 250 – 500 mg orally once daily for 1 – 2 weeks, then maintenance treatment is 250 mg orally once 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 twice daily	• Titrate up gradually to minimize side effects • Initiate at 300 mg on day one and increase by 300 mg daily as tolerated to target of 1,800 mg daily, administered in three divided doses
Alternative Dosing Schedules	• 25 mg once or twice daily with meals to reduce nausea, especially during the first week • 100 mg every other day or 150 mg every three days			• Reduce dose to 125 mg to reduce side effects • For monitored administration, consider giving 500 mg on Monday, Wednesday, and Friday	• One-half the usual starting dose and maintenance dose in patients with moderate-severe renal impairment • Dose adjustment may be necessary in elderly patients with impaired renal function (CrCl <70 mL/min)	

Topic Area	Naltrexone Oral	Naltrexone Injectable	Acamprosate	Disulfiram	Topiramate	Gabapentin
Dosing in Special Populations	• Mild – moderate hepatic impairment: use with caution • Severe hepatic impairment: Do not use	• Mild renal insufficiency (CrCl 50 – 80 mL/min): No dosage adjustment necessary • CrCl <50 mL/min: use with caution	• Moderate renal insufficiency (CrCl 30 – 50 mL/min): 333 mg thrice daily • Do not administer to patients with severe renal insufficiency (CrCl ≤30 mL/min)		• CrCl <70 mL/min: 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 <1,800 mg daily when CrCl <60 mL/min
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 • GI: Abdominal pain, anorexia	• CNS: Dizziness, drowsiness, ataxia, fatigue, peripheral edema • GI: Diarrhea, nausea/vomiting, abdominal pain
Drug Interactions	• Opioid-containing medications, including OTC preparations, antidiarrheal, and cough and cold remedies	• Opioid-containing medications, including OTC preparations, antidiarrheal, and cough and cold remedies		• Alcohol containing medications, including OTC preparations • Metronidazole • Phenytoin, warfarin, oral anticoagulants isoniazid, rifampin, 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

Topic Area	Naltrexone Oral	Naltrexone Injectable	Acamprosate	Disulfiram	Topiramate	Gabapentin
Monitoring	• Repeat liver transaminase levels at six and 12 months and then every 12 months thereafter • Discontinue and consider alternatives if no detectable benefit after an adequate trial (50 mg daily for three months)	• Repeat liver transaminase levels at six and 12 months and then every 12 months thereafter • Discontinue if there is no detectable benefit within three months	• Monitor serum creatinine/CrCl, particularly in the elderly and in patients with renal insufficiency • Mental status/suicidality	• Repeat liver transaminase levels within the first month, then monthly for first three months, and periodically thereafter as indicated • Consider discontinuation in event of relapse or when patient is not available for supervision and counseling • Counsel patient to report immediately if fatigue, abdominal pain, fever, nausea, jaundice or clay colored stools occur (early signs of liver toxicity)	• Monitor serum creatinine/CrCl periodically, particularly in patients with renal insufficiency and in elderly patients • Monitor for change in behavior which might indicate suicidal thoughts or depression • Discontinue and consider alternatives if no detectable benefit after an adequate trial (300 mg daily for three 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 and consider alternatives if no detectable benefit from at least 900 mg daily for 2 – 3 months

Topic Area	Naltrexone Oral	Naltrexone Injectable	Acamprosate	Disulfiram	Topiramate	Gabapentin
Patient Education	• Discuss compliance enhancing methods • Side effects, if any, tend to occur early in treatment and can typically resolve within 1 – 2 weeks after dosage adjustment • Take dose with food to mitigate risk for side effects (GI upset)	• 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	• Report any new or worsening depression or suicidal thinking • Food may decrease bioavailability • Do not double the doses if earlier doses are missed	• 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 • Counsel patient to report immediately if fatigue, abdominal pain, fever, nausea, jaundice or clay colored stools occur (early signs of liver toxicity)	• 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	• Take first dose on first day at bedtime to minimize somnolence and dizziness • Caution patients about performing tasks requiring mental alertness
	• Carry wallet card alerting medical personnel they are taking naltrexone • If signs and symptoms of hepatic toxicity (e.g., yellowing of the skin, lethargy) occur, contact provider immediately • 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; BAL: blood alcohol level; Cmax: maximum concentration; CNS: central nervous system; CrCl: creatinine clearance; DSM: Diagnostic and Statistical Manual of Mental Disorders; GI: gastrointestinal; HCG: human chorionic gonadotropin; m: meter(s); mg: milligram(s); min: minute(s); mL: milliliter(s); NICU: neonatal intensive care unit; OTC: over the counter; SGA: small for gestational age; vs.: versus

A. Other Medications for AUD: Not Recommended

Two RCTs of baclofen for AUD provided low quality evidence for the medication's efficacy but had inconsistent findings regarding alcohol consumption outcomes.(187) 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 for AUD. Two very small trials provided low to moderate quality evidence for a positive effect on alcohol consumption.(187) 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.(187, 353)

Although not included in this CPG's systematic evidence review, an RCT by Simpson et al. (2018) evaluated prazosin in individuals with AUD but without PTSD.(354) It demonstrated reduced alcohol consumption associated with prazosin compared to placebo over time. Another RCT by O'Malley et al. (2018) demonstrated reduced heavy drinking and smoking abstinence among men assigned to the varenicline group compared to men in the placebo group, with less effect on drinking among women in the active condition.(355)

Table B-2. Pharmacotherapy for Opioid Use Disorder[d]

Topic Area	Methadone	Buprenorphine/Naloxone or Buprenorphine	Buprenorphine Depot Injectable	Naltrexone Injectable
Indications	• OUD (DSM diagnosis) and patient meets Federal OTP Standards (see 42 C.F.R. § 8.12)	• OUD (DSM diagnosis)	• OUD (DSM diagnosis) in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of seven days	• OUD (DSM diagnosis) with: 1. Pretreatment abstinence from opioids and no signs of opioid withdrawal, and; 2. Willingness to receive monthly injections
Contraindications	• Hypersensitivity	• Hypersensitivity	• Hypersensitivity	• Receiving opioid agonists • Physiologic opioid dependence with use within past seven days • Acute opioid withdrawal • Failed naloxone challenge test • Positive urine opioid screen • Acute hepatitis or liver failure • Hypersensitivity • Inadequate muscle mass

[d] While this table provides evidence-based suggestions for dosage and administration of medications for OUD and AUD, some strategies (e.g., microdosing) are not explained here. Providers should use clinical judgment and engage in shared decision making to determine appropriate initiation, titration, and dosage strategy for each patient.

Topic Area	Methadone	Buprenorphine/Naloxone or Buprenorphine	Buprenorphine Depot Injectable	Naltrexone Injectable
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) and increased monitoring and vigilance would be appropriate • Use of opioid antagonists (e.g., parenteral naloxone, oral or parenteral nalmefene, naltrexone) • Abrupt discontinuation or rapid dose taper may result in opioid withdrawal syndrome • Neonatal withdrawal has been reported following use of buprenorphine by pregnant women • Multiple drug interactions. See *Drug Interactions* below for more details.	• Buprenorphine/naloxone may precipitate withdrawal in patients on full agonist opioids • Buprenorphine can be misused in a similar manner to other opioids. Clinical monitoring appropriate to the patient's level of stability is essential. • Use caution in patients with respiratory, liver, or renal insufficiency • Concurrent benzodiazepines or other CNS depressants, including active AUD (potential respiratory depression) and increased monitoring and vigilance, would be appropriate • Use of opioid antagonists (e.g., parenteral naloxone, oral or parenteral nalmefene, naltrexone) • Abrupt discontinuation or rapid dose taper may result in opioid withdrawal syndrome • Neonatal withdrawal has been reported following use of buprenorphine by pregnant women • Transmucosal buprenorphine/naloxone is preferred for maintenance over transmucosal buprenorphine alone given the increased risk of diversion and misuse	• Buprenorphine may precipitate withdrawal in patients on full agonist opioids. Verify that patient is clinically stable on transmucosal buprenorphine before injecting. • Serious harm or death if administered IV. Only available through the REMS Program. Healthcare settings and pharmacies that order and dispense must be certified in this program and comply with the REMS requirements • Can only be administered by a healthcare provider. • Use caution in patients with respiratory, liver, or renal insufficiency • Concurrent benzodiazepines or other CNS depressants, including active AUD (potential respiratory depression); buprenorphine can still be used with proper monitoring • Use of opioid antagonists (e.g., parenteral naloxone, oral or parenteral nalmefene, naltrexone) • Abrupt discontinuation may result in opioid withdrawal syndrome • Neonatal withdrawal has been reported following use of buprenorphine by pregnant women	• Active liver disease • Uncertain effects (no data) in moderate-severe renal insufficiency • Injection site reactions • Use intramuscular injections with caution in patients with thrombocytopenia or coagulation disorders

Topic Area	Methadone	Buprenorphine/Naloxone or Buprenorphine	Buprenorphine Depot Injectable	Naltrexone Injectable
Baseline Evaluation	• Consider baseline electrocardiogram and physical examination for patients at risk for QT prolongation or arrhythmias	• Objective and clear signs of withdrawal should be evident to avoid precipitating withdrawal		• 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 drug testing
Dosage and Administration	• Initial dose: 20 – 30 mg single dose, maximum 40 mg first day dose • To make same-day dosing adjustments, have the patient wait 2 – 4 hours for further evaluation when peak levels have been reached; provide an additional 5 – 10 mg if withdrawal symptoms have not been suppressed or if symptoms reappear • 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 • Administer orally in single dose • Individualize dosing regimens (avoid same fixed dose for all patients)	Suboxone (buprenorphine/naloxone sublingual tablet or film): • Induction dose: 2 – 4 mg first dose, up to 8 mg (film) first day • 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 • One SUBOXONE® (buprenorphine and naloxone) 8 mg/2 mg sublingual tablet provides equivalent buprenorphine exposure to one SUBUTEX® (buprenorphine HCl) 8 mg sublingual tablet or one Bunavail® (buprenorphine and naloxone) 4.2 mg/0.7 mg buccal film or one Zubsolv® (buprenorphine and naloxone) 5.7 mg/1.4 mg sublingual tablet	• Should only be prepared and administered by healthcare providers • Only following induction and dose-adjustment on a transmucosal buprenorphine-containing product delivering the equivalent of 8 – 24 mg of buprenorphine daily for at least seven days • 300 mg monthly for the first two months followed by a maintenance dose of 100 mg monthly by abdominal subcutaneous injection (doses should be given no sooner than 26 days apart) • Consider maintenance dose of 300 mg monthly for patients who do not demonstrate satisfactory clinical response on 100 mg monthly	• Should only be prepared and administered by healthcare providers • 380 mg once monthly by deep intramuscular gluteal injection

Topic Area	Methadone	Buprenorphine/Naloxone or Buprenorphine	Buprenorphine Depot Injectable	Naltrexone Injectable
Alternative Dosing Schedules	• Give in divided daily doses based on peak and trough serum levels that document rapid metabolism that justifies divided doses	• Give equivalent weekly maintenance dose divided over extended dosing intervals (twice or thrice weekly or every 2, 3, or 4 days)		
Dosing in Special Populations	• Renal or hepatic impairment: Reduce dose • Elderly or debilitated: Reduce dose • For concurrent chronic pain, consider dividing total daily dose into twice or thrice daily administration	• Hepatic impairment: Reduce dose • For concurrent chronic pain, consider dividing total daily dose into twice or thrice daily administration	• Hepatic impairment: Serum buprenorphine levels persist and do not rapidly decline, therefore patients with moderate-severe hepatic impairment are not candidates for treatment with the monthly depot injection	• Mild renal insufficiency (CrCl 50 – 80 mL/min): No dosage adjustment necessary • Uncertain effects (no data) in moderate-severe renal insufficiency; use with caution since naltrexone and its primary metabolite are primarily excreted in urine
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: Oral hypoesthesia, glossodynia, oral mucosal erythema, headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, pain, and peripheral edema	• Major: Hepatitis, hepatic failure, respiratory depression, arrhythmia associated with prolonged QT interval, serotonin syndrome • Common: Constipation, headache, nausea, injection site pruritus, vomiting, increased hepatic enzymes, fatigue, and injection site pain	• Major: Eosinophilic pneumonia, depression, suicidality • Common: Injection site reaction, injection site tenderness, injection site induration, nausea, headache, asthenia

Topic Area	Methadone	Buprenorphine/Naloxone or Buprenorphine	Buprenorphine Depot Injectable	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 • CNS depressants: May enhance the CNS depressant effect of methadone • QT-prolonging agents: Avoid use in patients taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide)	• 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: CYP-3A4 inhibitors (azole antifungals such as ketoconazole, macrolide antibiotics such as erythromycin, and HIV protease inhibitors such as ritonavir and atazanavir, as well as some NNRTIs such as delavirdine) • Opioid agonist: Buprenorphine/naloxone or buprenorphine may precipitate withdrawal • Opioid antagonists may precipitate withdrawal • CNS depressants: May enhance the CNS depressant effect of buprenorphine • QT-prolonging agents: Avoid use in patients taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide)	• Drugs that reduce serum buprenorphine level: CYP3A4 inducers (rifampin, carbamazepine, phenytoin, phenobarbital, and some NNRTIs such as efavirenz, nevirapine, and etravirine) • Drugs that increase serum buprenorphine level: CYP-3A4 inhibitors (azole antifungals such as ketoconazole, macrolide antibiotics such as erythromycin, and HIV protease inhibitors such as ritonavir and atazanavir, as well as some NNRTIs such as delavirdine) • Opioid agonist: Buprenorphine may precipitate withdrawal • Opioid antagonists may precipitate withdrawal • CNS depressants: May enhance the CNS depressant effect of buprenorphine • QT-prolonging agents: Avoid use in patients taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide)	• Opioid-containing medications, including OTC preparations • Thioridazine (increased lethargy and somnolence)

Topic Area	Methadone	Buprenorphine/Naloxone or Buprenorphine	Buprenorphine Depot Injectable	Naltrexone Injectable
Monitoring	• Signs of respiratory and CNS depression	• Signs of CNS depression	• Signs of CNS depression	• Repeat liver transaminase levels at six and 12 months and then every 12 months thereafter
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 • May affect perioperative pain control; discuss with provider	• 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 • Strongly advise patient to continue in long-term buprenorphine maintenance • This drug is given into the fatty part of the abdominal skin only; if given other ways (into a vein or muscle), this can be deadly • Advise patients of the importance of instructing their family members, in the event of emergency, to inform the treating provider or ER staff that the patient is being treated with monthly buprenorphine depot injection • May affect perioperative pain control; discuss with provider	• 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 • 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; C.F.R.: Code of Federal Regulations; CNS: central nervous system; CrCl: creatinine clearance; DSM: Diagnostic and Statistical Manual of Mental Disorders; ER: emergency room; HCG: human chorionic gonadotropin; IV: intravenous; LFTs: liver function tests; MAOIs: monoamine oxidase inhibitors; mg: milligram(s); min: minute(s); mL: milliliter(s); NNRTIs: non-nucleoside reverse transcriptase inhibitors; OTC: over the counter; 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; REMS: Risk Evaluation and Mitigation Strategy; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants

Table B-3. Sedative-hypnotic Conversion

Generic Name	Approximate Equivalents to Diazepam 10 mg or Phenobarbital 30 mg[a]	Time to Peak Plasma level (in Hours)	Half-life Parent Drug (in Hours)[b]	Metabolite Activity (Maximal Half-life in Hours)[c]
Alprazolam	1 mg	1 – 2	12 ± 2	Inactive
Chlordiazepoxide	25 mg	2 – 4	24 – 48	Active (up to 96)
Clonazepam	1 mg	1 – 4	30 – 40	Inactive
Clorazepate	15 mg	1 – 2	2 ± 0.9	Active (40 – 50)
Diazepam	10 mg	1 – 2	43 ± 13	Active (50 – 100)
Estazolam	1 mg	2	10 – 24	Inactive
Flurazepam	15 mg	0.5 – 1.0	2.3	Active (up to 100)
Lorazepam	2 mg	1 – 6	10 – 20	Inactive
Oxazepam	30 mg	2 – 4	5 – 20	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)

[a] Withdrawal doses of diazepam or phenobarbital are those sufficient to suppress most withdrawal symptoms and may not reflect therapeutic dose equivalency.

[b] Half-life of active metabolite(s) may differ.

[c] Primary route of barbiturate elimination is renal excretion.

Abbreviation: mg: milligrams

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 therapy (CBT)	√	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 (IDC)	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	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; BCT: behavioral couples therapy; CBT: cognitive behavioral therapy; CM: contingency management; CRA: community reinforcement approach; IDC: individual drug counseling; MET: motivational enhancement therapy; SUD: substance use disorders; TSF: 12-step facilitation

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, observed taking of Antabuse or other addiction medication, 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.(356, 357)

B. Cognitive Behavioral Therapy

Cognitive behavioral 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, improve 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 the session, including scheduled activities, self-monitoring, thought recording and challenging, and interpersonal skills practice.(358-361)

C. Community Reinforcement Approach

Community reinforcement approach is a comprehensive cognitive-behavioral intervention for the treatment of SUD that focuses on environmental contingencies that impact and influence the patient's behavior. Developed under 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. Community reinforcement approach 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. In research studies, it has often been combined with CM, with incentives provided for drug abstinence.(362, 363)

D. Contingency Management

Contingency management 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 that vary in their reinforcing value from simple praise to vouchers worth $1 – 100. Schedules (fixed or intermittent) and magnitude of reinforcement have varied and have implications for overall cost and effectiveness of clinical implementation.(364)

E. Individual Drug Counseling

The approach to IDC is manualized (365) 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 participation (e.g., AA, NA).

F. Motivational Enhancement Therapy

Motivational enhancement therapy is a less intensive form of specialized psychosocial intervention for patients with SUD. It uses principles of 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. Motivational enhancement therapy 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. It should be noted that MET is not a BI, as it is provided over four 60 minute sessions.(366)

G. 12-step Facilitation

12-step facilitation 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).(367) Network support based on TSF engages patients in pro-recovery organizations other than AA and has proved to be efficacious in randomized trials.(317, 318)

Appendix D: Evidence Table

Table D-1. Evidence Table[a,b,c,d]

Recommendation	2015 Strength of Recommendation	Evidence	2021 Strength of Recommendation	Recommendation Category
1. For patients in general medical and mental healthcare settings, we recommend screening for unhealthy alcohol use periodically using the three-item Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) or Single Item Alcohol Screening Questionnaire (SASQ).	Strong for	(101, 102) **Additional references**: (31, 49, 103-114)	Strong for	Not reviewed, Amended
2. For patients without documented alcohol use disorder who screen positive for unhealthy alcohol use, we suggest providing a single initial brief intervention regarding alcohol-related risks and advising to abstain or drink within established limits for daily and weekly consumption.	Strong for	(102, 115-117)	Weak for	Not reviewed, Amended
3. There is insufficient evidence to recommend for or against screening for drug use disorders in primary care to facilitate enrollment in treatment.	Not applicable	(118) **Additional references:** (119, 120)	Neither for nor against	Reviewed, New-added

[a] 2015 Strength of Recommendation column: The 2015 VA/DoD SUD CPG was developed using the GRADE approach to determine the strength of each recommendation. Inclusion of more than one 2015 strength of recommendation indicates that more than one 2015 VA/DoD SUD CPG recommendation is covered by the 2021 recommendation. "Not applicable" indicates that the 2021 VA/DoD SUD CPG recommendation was a new recommendation, and therefore does not have an associated 2015 strength of recommendation.

[b] Evidence column: The first set of references listed in each row in the evidence column constitutes the evidence base for the recommendation. To be included in the evidence base for a recommendation, a reference needed to be identified through a systematic evidence review carried out as part of the initial development or update of this CPG. The second set of references in the evidence column (called "Additional References") includes references that provide additional information related to the recommendation, but which were not identified through a systematic evidence review. These references were, therefore, not included in the evidence base for the recommendation and did not influence the strength and direction of the recommendation.

[c] 2021 Strength of Recommendation column: The 2021 VA/DoD SUD CPG was developed using the GRADE approach to determine the strength of each recommendation. Refer to the Grading Recommendations section for more information.

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

Recommendation	2015 Strength of Recommendation	Evidence	2021 Strength of Recommendation	Recommendation Category
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.	Neither for nor against	**Additional references**: (121)	Neither for nor against	Not reviewed, Amended
5. For the treatment of moderate-severe alcohol withdrawal, we recommend using benzodiazepines with adequate monitoring.	Strong for	(122) **Additional references:** (123-126)	Strong for	Not reviewed, Amended
6. For managing mild-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	(122) **Additional references:** (127-136)	Weak for	Not reviewed, Not changed
7. For patients with opioid use disorder, we recommend against withdrawal management, without planned ongoing pharmacotherapy treatment, due to high risk of relapse and overdose (see Recommendations 16, 17, and 18).	Strong against	(145, 154) **Additional references**: (137-144, 146-153)	Strong against	Not reviewed, Amended
8. For patients with opioid use disorder for whom opioid withdrawal management is indicated, we suggest using: • Buprenorphine/naloxone (in any setting); or • Methadone or buprenorphine/naloxone (in inpatient or accredited Opioid Treatment Programs) (see Recommendation 17).	Strong for	(156, 157, 159-170) **Additional references**: (137, 149, 155, 158, 172)	Weak for	Reviewed, New-replaced
9. For patients with opioid use disorder for whom withdrawal management is indicated and for whom methadone and buprenorphine are contraindicated, unacceptable, or unavailable, we suggest offering clonidine or lofexidine as a second-line agent for opioid withdrawal management (see Recommendation 17).	Strong for	(173-177)	Weak for	Reviewed, New-replaced
10. For patients in need of withdrawal management for benzodiazepines, we recommend gradually tapering benzodiazepines.	Weak for	**Additional references**: (178-181)	Strong for	Reviewed, New-replaced

Recommendation	2015 Strength of Recommendation	Evidence	2021 Strength of Recommendation	Recommendation Category
11. There is insufficient evidence to recommend the use of adjunctive medications for the treatment of benzodiazepine withdrawal.	Not applicable	(182)	Neither for nor against	Reviewed, New-added
12. For patients with moderate-severe alcohol use disorder, we recommend offering one of the following medications: • Naltrexone (oral or extended-release) • Topiramate	Strong for	(183, 185, 187) **Additional references**: (184, 186)	Strong for	Not reviewed, Amended
13. For patients with moderate-severe alcohol use disorder, we suggest offering one of the following medications: • Acamprosate • Disulfiram	Strong for	(187, 188) **Additional references**: (186)	Weak for	Not reviewed, Amended
14. For patients with moderate-severe alcohol use disorder for whom first-line pharmacotherapy is contraindicated or ineffective, we suggest offering gabapentin.	Weak for	(187, 189) **Additional references**: (190-193)	Weak for	Not reviewed, Not changed
15. For patients with alcohol use disorder, we suggest one or more of the following interventions, considering patient preference and availability: • Behavioral couples therapy • Cognitive behavioral therapy • Community reinforcement approach • Motivational enhancement therapy • 12-step facilitation	Strong for	(194-196, 198-204) **Additional references**: (197, 205, 206)	Weak for	Not reviewed, Amended
16. For patients with opioid use disorder, we recommend one of the following strategies: • Buprenorphine/naloxone in any setting; or • Methadone or buprenorphine/naloxone provided through an accredited Opioid Treatment Program	Strong for	(157, 214) **Additional references**: (64, 138, 141, 142, 145, 155, 156, 207-213, 215-236)	Strong for	Reviewed, Amended
17. For patients with opioid use disorder, we suggest offering extended-release naltrexone (IM).	Strong for	(237-240)	Weak for	Reviewed, New-replaced

Recommendation	2015 Strength of Recommendation	Evidence	2021 Strength of Recommendation	Recommendation Category
18. There is insufficient evidence to recommend any one of the different FDA-approved formulations or routes of delivery of buprenorphine over another.	Not applicable	(222, 241)	Neither for nor against	Reviewed, New-added
19. There is insufficient evidence to recommend for or against oral naltrexone for the treatment of opioid use disorder.	Neither for nor against	(237, 242)	Neither for nor against	Reviewed, Not changed
20. For patients receiving medication treatment for opioid use disorder, there is insufficient evidence to recommend for or against any specific psychosocial interventions in addition to addiction-focused medical management.	Neither for nor against	(61, 244-248, 252-255) **Additional references:** (249-251)	Neither for nor against	Reviewed, Amended
21. 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.	Neither for nor against	(256-259)	Neither for nor against	Not reviewed, Amended
22. There is insufficient evidence to recommend for or against the use of pharmacotherapy in the treatment of cannabis use disorder.	Neither for nor against	(95, 262-265) **Additional references:** (260, 261, 266, 267)	Neither for nor against	Reviewed, Not changed
23. For patients with cannabis use disorder, we suggest one of the following interventions as initial treatment, considering patient preference and availability: • Cognitive behavioral therapy • Motivational enhancement therapy • Combined cognitive behavioral therapy/motivational enhancement therapy	Weak for	(268-270)	Weak for	Reviewed, Amended
24. We suggest against the use of a brief intervention (i.e., 60 minutes or less) for the treatment of cannabis use disorder.	Not applicable	(271)	Weak against	Reviewed, New-added
25. There is insufficient evidence to recommend for or against the use of any pharmacotherapy for the treatment of cocaine use disorder or amphetamine/methamphetamine use disorder.	Neither for nor against	(273-279, 286) **Additional references**: (272, 280-285, 287, 288)	Neither for nor against	Reviewed, Amended

Recommendation	2015 Strength of Recommendation	Evidence	2021 Strength of Recommendation	Recommendation Category
26. For patients with cocaine use disorder, we recommend one or more of the following interventions as initial treatment, considering patient preference and availability: • Cognitive behavioral therapy • Recovery-focused behavioral therapy (i.e., individual drug counseling and community reinforcement approach) • Contingency management in combination with another behavioral intervention considering patient preference and availability	Strong for	(289-291, 293-296, 299-307) **Additional references**: (292, 297, 298, 308, 309)	Strong for	Not reviewed, Amended
27. For patients with amphetamine/methamphetamine use disorder, we suggest offering contingency management as initial treatment in combination with another behavioral intervention, considering patient preference and availability.	Weak for	(310) **Additional references**: (308, 309, 311)	Weak for	Not reviewed, Amended
28. For patients with alcohol use disorder 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 availability: • Peer linkage • Network support • 12-step facilitation	Strong for	(312, 313) **Additional references**: (314-318)	Strong for	Reviewed, New-replaced
29. For patients with drug use disorders in early recovery or following relapse, we suggest promoting active involvement in group mutual help programs using one of the following systematic approaches, considering patient preference and availability: • Peer linkage • 12-step facilitation	Strong for	(319-321) **Additional references**: (316)	Weak for	Reviewed, New-replaced
30. There is insufficient evidence to recommend for or against mindfulness-based therapies for the treatment of substance use disorders.	Not applicable	(322-330) **Additional references:** (331)	Neither for nor against	Reviewed, New-added

Recommendation	2015 Strength of Recommendation	Evidence	2021 Strength of Recommendation	Recommendation Category
31. We suggest using technology-based interventions (e.g., automated text/voice messaging, smartphone apps), in addition to usual care, for alcohol use disorder.	Not applicable	(332-337) **Additional references**: (338)	Weak for	Reviewed, New-added
32. There is insufficient evidence to recommend for or against using technology-based interventions (e.g., automated text/voice messaging, smartphone apps), in addition to usual care, for substance use disorders other than alcohol use disorder.	Not applicable	(332-337)	Neither for nor against	Reviewed, New-added
33. We suggest the use of structured telephone-based care as an adjunct to usual care for substance use disorders.	Not applicable	(339-341)	Weak for	Reviewed, New-added
34. There is insufficient evidence to recommend for or against the use of telemedicine-delivered treatment for substance use disorders.	Not applicable	(342) **Additional references:** (343)	Neither for nor against	Reviewed, New-added
35. There is insufficient evidence to recommend for or against the use of computer-delivered behavioral treatments, either alone or in combination with usual care, for substance use disorders.	Not applicable	(344-351)	Neither for nor against	Reviewed, New-added

Appendix E: 2015 Recommendation Categorization Table

Table E-1. 2015 SUD CPG Recommendation Categorization Table[a,b,c,d,e,f]

2015 CPG Recommendation #	2015 CPG Recommendation Text	2015 CPG Strength of Recommendation	2015 CPG Recommendation Category	2021 CPG Recommendation Category	2021 CPG 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	Not reviewed, Amended	1
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	Not reviewed, Amended	2
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	Not reviewed, Deleted	–
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.	Neither for nor against	Reviewed, New-replaced	Not reviewed, Amended	4

[a] 2015 CPG Recommendation # column: This indicates the recommendation number of the recommendation in the 2015 VA/DoD SUD CPG.
[b] 2015 CPG Recommendation Text column: This contains the wording of each recommendation from the 2015 VA/DoD SUD CPG.
[c] 2015 CPG Strength of Recommendation column: The 2015 VA/DoD SUD CPG used the GRADE approach to determine the strength of each recommendation. The strength of recommendations in the 2015 VA/DoD SUD CPG were: Strong for, Weak for, N/A, Weak against, or Strong against.
[d] 2015 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2015 VA/DoD SUD CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.
[e] 2021 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2021 VA/DoD SUD CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.
[f] 2021 CPG Recommendation # column: For recommendations that were carried forward to the 2015 VA/DoD SUD CPG, this column indicates the new recommendation(s) to which they correspond.

2015 CPG Recommendation #	2015 CPG Recommendation Text	2015 CPG Strength of Recommendation	2015 CPG Recommendation Category	2021 CPG Recommendation Category	2021 CPG Recommendation #
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	Not reviewed, Amended	12, 13
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	Not reviewed, Not changed	14
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	Not reviewed, Amended	15
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	Reviewed, Amended	16
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	Not reviewed, Deleted	–
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	Not reviewed, Deleted	–

2015 CPG Recommendation #	2015 CPG Recommendation Text	2015 CPG Strength of Recommendation	2015 CPG Recommendation Category	2021 CPG Recommendation Category	2021 CPG Recommendation #
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	Reviewed, New-replaced	17
12	There is insufficient evidence to recommend for or against oral naltrexone for treatment of opioid use disorder.	Neither for nor against	Reviewed, New-replaced	Reviewed, Not changed	19
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	Not reviewed, Deleted	–
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.	Neither for nor against	Reviewed, New-replaced	Reviewed, Amended	20
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	Not reviewed, Deleted	–
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.	Neither for nor against	Reviewed, New-replaced	Not reviewed, Amended	21
17	There is insufficient evidence to recommend for or against the use of pharmacotherapy in the treatment of cannabis use disorder.	Neither for nor against	Reviewed, New-added	Reviewed, Not changed	22
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	Reviewed, Amended	23
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.	Neither for nor against	Reviewed, New-added	Reviewed, Amended	25

2015 CPG Recommendation #	2015 CPG Recommendation Text	2015 CPG Strength of Recommendation	2015 CPG Recommendation Category	2021 CPG Recommendation Category	2021 CPG 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 (i.e. General Drug Counseling and Community Reinforcement Approach) • Contingency Management in combination with one of the above	Strong for	Reviewed, New-replaced	Not reviewed, Amended	26, 27
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	Reviewed, New-replaced	28, 29
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	Not reviewed, Deleted	–
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	Not reviewed, Deleted	–
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	Not reviewed, Deleted	–
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	Not reviewed, Deleted	–

2015 CPG Recommendation #	2015 CPG Recommendation Text	2015 CPG Strength of Recommendation	2015 CPG Recommendation Category	2021 CPG Recommendation Category	2021 CPG 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	Not reviewed, Deleted	–
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	Not reviewed, Deleted	–
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	Not reviewed, Deleted	–
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	Not reviewed, Deleted	–

2015 CPG Recommendation #	2015 CPG Recommendation Text	2015 CPG Strength of Recommendation	2015 CPG Recommendation Category	2021 CPG Recommendation Category	2021 CPG 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	Not reviewed, Amended	5
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	Not reviewed, Not changed	6
32	We recommend against using alcohol as an agent for medically supervised withdrawal.	Strong against	Not reviewed, Amended	Not reviewed, Deleted	–
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	Not reviewed, Amended	7
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	Reviewed, New-replaced	8
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	Reviewed, New-replaced	9
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	Reviewed, New-replaced	10

Appendix F: Patient Focus Group Methods and Findings

A. Methods

VA and DoD Leadership recruited participants for the focus group, with support from the Champions, other Work Group members, and individuals at the patient focus group location as needed. While participant recruitment focused on eliciting a range of perspectives likely to be relevant and informative in the CPG development process, patient focus group participants were not intended to be a representative sample of VA and DoD patients. Participants were not incentivized for their participation or reimbursed for travel expenses.

The Work Group, with support from the Lewin Team, identified topics on which patient input was important to consider in developing the CPG. The Lewin Team developed and the Work Group approved and patient focus group guide covering these topics. The focus group facilitator led the discussion used the guide to elicit the patients' perspectives about their treatment and overall care. Given the limited time and the range of interests of the focus group participants, not all questions were addressed.

B. Patient Focus Group Findings

a. *Participants noted their development of SUD resulted from or was related to various life events, symptoms, behaviors, and other disorders they experienced including the loss of a family member, anxiety, depression, excessive shopping, binge drinking, excessive anger, and PTSD.*

- Many participants described their SUD as a result of or related to other mental health issues and life events.
- Some participants recalled feeling easily overwhelmed and experiencing negative emotions persistently before being diagnosed with an SUD including anger, anxiety, and depression.

b. Participants described success with holistic and multi-faceted inpatient treatment for SUD. They specifically commended the use of cognitive behavioral therapy, mindfulness meditation, and pharmacotherapy.

- Participants highlighted the success of specific therapies such as mindfulness meditation and pharmacotherapy initiated in inpatient settings to treat their SUD.
- Participants considered relapses to be part of the course of illness and eventually improvement and recovery.
- Participants stated their SUD greatly improved due to holistic or multi-faceted treatments.

c. Participants expressed frustration with the lack of coordination and inadequate transitions between inpatient and outpatient treatment settings. In particular, patients had to initiate care and there was a significant time lag to access outpatient services.

- Participants noted significant difficulty in transitioning from inpatient to outpatient therapy.
- Participants also noted a lack of information from providers regarding long-term outpatient programs and the lack of a clearly developed after-care plan.

d. Participants remarked that stigma related to SUD in the culture of the military contributes to the development of SUD disorders and the unwillingness to obtain treatment. However, the development and use of educational resources for the military population can increase knowledge of and counteract bias around SUD.

- Participants noted that the demands of being in the military, and the high prevalence of drinking, use of substances, and the stigma associated with recognizing and treating SUD all serve as barriers to recognizing and promoting treatment among active duty Service Members.
- Participants expressed concern about the lack of education providers, families, and active duty Service Members had on SUD and SUD treatment.

Appendix G: Alternative Text Description of Algorithm

The following outline narratively describes the Management of Substance Use Disorders algorithm. An explanation of the purpose of the algorithm and description of the various shapes used within the algorithm can be found in the Algorithm section. The sidebars referenced within this outline can also be found in the Algorithm section.

A. Module A: Screening and Treatment

1. Module A begins with Box 1, in the shape of a rounded rectangle: "All patients seen in VA or DoD healthcare settings"
2. Box 1 connects to Box 2, in the shape of a hexagon, and asks the question: "Is acute medical or mental health stabilization required?"
    a. If the answer is "Yes" to Box 2, then continue to Box 3, in the shape of an oval: "Refer to appropriate setting to manage or stabilize (see Module B)"
    b. If the answer is "No" to Box 2, then Box 4, in the shape of a hexagon, asks the question: "Are there signs and symptoms of any substance use disorder other than alcohol or tobacco?"
        i. If the answer is "Yes" to Box 4, then Box 11, in the shape of a hexagon, asks the question: "Is treatment or further evaluation indicated and acceptable to patient?"
        ii. If the answer is "Yes" to Box 11, then continue to Box 14 in the shape of a rectangle: "Offer specialty referral or management in primary care"
            1. If the answer is "No" to Box 11, then continue to Box 12 in the shape of a rectangle: "Follow-up during future visits as indicated"
3. If the answer is "No" to Box 4, then continue to Box 5, in the shape of a rectangle: "Screen annually for unhealthy alcohol use using the AUDIT-C"
    a. Box 5 connects to Box 6, in the shape of a hexagon, and asks the question: "Does the patient screen positive or drink despite contraindications?"
        i. If the answer is "Yes" to Box 6, then Box 7, in the shape of a hexagon, asks the question: "Confirm current alcohol consumption: drinking above recommended limits? (see Sidebar 1)"
        ii. If the answer is "Yes" to Box 7, then Box 9, in the shape of a hexagon, asks the question: "Does the patient have AUD per DSM-5 criteria?"
        iii. If the answer is "Yes" to Box 9, then Box 11, in the shape of a hexagon, asks the question: "Is treatment or further evaluation indicated and acceptable to patient?"

iv. If the answer is "Yes" to Box 11, then continue to Box 14 in the shape of a rectangle: "Offer specialty referral or management in primary care"

1. If the answer is "No" to Box 11, then continue to Box 12 in the shape of a rectangle: "Follow-up during future visits as indicated"
2. If the answer is "No" to Box 9, then continue to Box 10 in the shape of a rectangle: "Provide brief intervention (see Sidebar 2)"
3. If the answer is "No" to Box 7, then continue to Box 8 in the shape of a rectangle: "Advise to stay below recommended limits"
4. If the answer is "No" to Box 6, then continue to Box 19, in the shape of a rectangle: "Screen annually for unhealthy alcohol use"

b. Box 10 connects to Box 12 in the shape of a rectangle: "Follow-up during future visits as indicated"

c. Box 12 connects to Box 13 in the shape of a hexagon and asks the question: "Indication for and a willingness to seek treatment?"

i. If the answer is "Yes" to Box 13, then continue to Box 14, in the shape of a rectangle "Offer specialty referral or management in primary care"

ii. Box 14 connects to Box 15 in the shape of a rectangle: "Complete the biopsychosocial assessment and determine diagnoses per DSM-5 criteria"

iii. Box 15 connects to Box 16 in the shape of a rectangle: "Develop and implement comprehensive treatment plan using shared decision making" which contains a bulleted list:

- If patient has OUD or is at high risk for opioid overdose, prescribe naloxone
- Offer/begin SUD focused pharmacotherapy if indicated (see Sidebars 3 and 4)
- Offer SUD focused psychosocial interventions if indicated (see Appendix C)
- Address psychosocial functioning and recovery environment (e.g., housing, supportive recovery environment, and employment)
- Manage medical and psychiatric co-occurring conditions if indicated (see Sidebar 5)
- Assess response to treatment; adjust treatment and follow-up frequency as clinically indicated; advise against discharge if poor response to treatment or relapse"

iv. Box 16 connects to Box 17 in the shape of a hexagon, and asks the question: "Is continued SUD treatment needed?"

1. If the answer is "Yes" to Box 17, then continue to Box 16 "Develop and implement comprehensive treatment plan using shared decision making"
2. If the answer is "No" to Box 17, then continue to Box 19 in the shape of a rectangle "Screen annually for unhealthy alcohol use"

v. If the answer is "No" to Box 13, then continue to Box 18 in the shape of a rectangle: "Provide feedback as appropriate". This connects back to Box 6.

B. Module B: Stabilization and Withdrawal

1. Module B begins with Box 20 in the shape of a rounded rectangle: "Patient using substance(s) who may require stabilization for withdrawal"
2. Box 20 connects to Box 21, in the shape of a rectangle: "Obtain history, physical examination, mental status examination, medication including over the counter, and laboratory tests as indicated"
3. Box 21 connects to Box 22, in the shape of a hexagon, and asks the question: "Need for urgent or emergent care for medical or psychiatric conditions?"
    a. If the answer is "Yes" to Box 22, then continue to Box 23, in the shape of a rectangle: "Provide appropriate care to stabilize medical or psychiatric condition; follow legal mandates; for DoD active duty: keep commanding officer informed"
    b. Box 23 connects to Box 24, in the shape of a rectangle: "Assess the severity of withdrawal symptoms using clinical judgment and standardized measures (e.g., CIWA-Ar for alcohol or COWS for opioids)"
    c. If the answer is "No" to Box 22, then continue to Box 24.
4. Box 24 connects to Box 25 in the shape of a hexagon, and asks the question: "Need for withdrawal management?"
    a. If the answer is "Yes" to Box 25, then Box 26 in the shape of a hexagon, asks the question: "Willingness to accept withdrawal management?"
    b. If the answer is "Yes" to Box 26, then Box 28, in the shape of a hexagon, asks the question: "Is inpatient withdrawal management required? (see Sidebar 6)"
    c. If the answer is "Yes" to Box 28, then continue to Box 29 in the shape of a rectangle "Admit to inpatient withdrawal management and if patient has OUD or is at high risk for opioid overdose, prescribe naloxone on discharge (see Sidebars 7 and 8)"
        i. If the answer is "No" to Box 28, then continue to Box 30 in the shape of a rectangle "Initiate ambulatory withdrawal management and if patient has OUD or is at high risk for opioid overdose, prescribe naloxone (see Sidebars 7 and 8)"

d. Box 30 connects to Box 31, in the shape of a hexagon, and asks the question: "Was withdrawal management successful?"
    i. Box 29 also connects to Box 31.
    ii. If the answer is "Yes" to Box 31, then Box 32, in the shape of a hexagon, asks the question: "Willingness to accept SUD treatment?"
    iii. If the answer is "Yes" to Box 32, then continue to Box 35 in the shape of an oval "Proceed to SUD treatment (see Module A - Box 4)"
        1. If the answer is "No" to Box 32, then continue to Box 34 in the shape of a rounded rectangle "Follow-up in general medical or mental healthcare or return to Box 1 as indicated"
        2. If the answer is "No" to Box 31, then continue to Box 33 in the shape of a rectangle "Assess barriers to successful withdrawal management". This connects back to Box 26.
e. If the answer is "No" to Box 26, then continue to Box 34 in the shape of a rounded rectangle "Follow-up in general medical or mental healthcare or return to Module A - Box 1 as indicated"
f. If the answer is "No" to Box 25, then continue to Box 27 in the shape of an oval "Return to Module A - Box 4"

Appendix H: Literature Review Search Terms and Strategy

A. EMBASE and Medline in EMBASE.com syntax (all KQs)

KQ	Set #	Concept	Strategy
KQ 1 (OUD medications); KQ 2 (OUD medication w/out psychological therapy); KQ 7 (opioid withdrawal)	#1	Population: OUD/ withdrawal	'opiate addiction'/exp OR 'opioid use disorder'/exp OR 'analgesic agent abuse'/exp OR (('drug abuse'/exp OR 'drug dependence'/exp OR 'narcotic dependence'/exp OR 'addiction'/exp OR 'withdrawal syndrome'/exp OR 'treatment withdrawal'/exp/mj OR 'drug withdrawal'/exp/mj) AND ('narcotic analgesic agent'/exp)) OR ((analgesic* OR codeine OR fentanyl OR heroin OR hydrocodone OR methadone OR morphine OR narcotic* OR opiate* OR opioid* OR opium OR oxycodone OR oxycontin OR percocet) NEAR/3 (abuse OR addict* OR dependen* OR disorder* OR withdraw* OR detox*)):ti,ab
	#2	Intervention and Comparison: Broad drug therapy terms	'drug therapy'/exp OR 'drug therapy'/lnk OR 'drug combination'/exp OR 'drug combination'/lnk OR 'drug administration'/exp OR 'drug administration'/lnk OR 'drug comparison'/exp OR 'drug comparison'/lnk OR 'drugs used in the treatment of addiction'/exp OR 'drug dependence treatment'/de OR 'maintenance drug dose'/de OR 'maintenance therapy'/de OR 'opiate substitution treatment'/de OR 'methadone treatment'/de OR pharmacotherap*:ti OR maintenance:ti OR ((medicine* OR medicat* OR drug*) NEAR/2 (therap* OR treat OR treatment*)):ti
	#3	Intervention and Comparison: Maintenance medications: Specific drugs and drug classes	'opiate receptor affecting agent'/exp/dd_dt OR 'opiate agonist'/exp/dd_dt OR 'opiate antagonist'/exp/dd_dt OR 'alpha adrenergic receptor stimulating agent'/exp/dd_dt OR 'clonidine'/exp/dd_dt OR 'gabapentin'/exp/dd_dt OR 'lofexidine'/exp/dd_dt OR 'tizanidine'/exp/dd_dt OR 'venlafaxine'/exp/dd_dt OR 'mirtazapine'/exp/dd_dt OR 'haloperidol'/exp/dd_dt OR (alpha NEAR/3 adrenergic) OR acetylmethadol OR buprenorphine OR clonidine OR guanabenz OR guanfacine OR LAAM OR levacetylmethadol OR lofexidine OR methadone OR naloxone OR naltrexone OR narcan* OR gabapentin OR hydromorphone OR tramadol OR tizanidine OR venlafaxine OR mirtazapine OR haloperidol
	#4	Combine concepts	#1 AND (#2 OR #3)
	#5	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table
KQ 3 (stimulant use disorder medications)	#1	Population: Stimulant/ amphetamine/ cocaine use disorder	'cocaine dependence'/exp OR 'methamphetamine dependence'/exp OR 'amphetamine dependence'/exp OR (('central stimulant agent'/exp OR 'amphetamine'/exp OR 'methamphetamine'/exp OR 'dexamphetamine'/exp OR 'cocaine'/exp OR midomafetamine/exp)) AND (('drug abuse'/exp OR 'drug dependence'/exp OR 'addiction'/exp OR 'withdrawal syndrome'/exp OR 'treatment withdrawal'/exp/mj OR 'drug withdrawal'/exp/mj)) OR ((amphetamine* OR atomoxetine OR cocaine OR lisdexamfetamine OR methamphetamine* OR methylphenidate OR dextroamphetamine OR dexamphetamine OR dexmethylphenidate OR Dexedrine OR Adderall OR mydayis OR stimulant* OR 'meth' OR analeptic* OR ecstasy OR MDMA OR oxymetazoline OR pseudoephedrine OR phenylephrine) NEAR/3 (abuse OR addict* OR dependen* OR disorder* OR misus* OR withdraw* OR detox*)):ti,ab
	#2	Intervention: Broad drug therapy terms	'drug therapy'/exp OR 'drug therapy'/lnk OR 'drug combination'/exp OR 'drug combination'/lnk OR 'drug administration'/exp OR 'drug administration'/lnk OR 'drug comparison'/exp OR 'drug comparison'/lnk OR 'drugs used in the treatment of addiction'/exp OR 'drug dependence treatment'/de OR 'maintenance drug dose'/de OR 'maintenance therapy'/de OR pharmacotherap*:ti OR maintenance:ti OR ((medicine* OR medicat* OR drug* OR prescription*) NEAR/3 (therap* OR treat OR treats OR treating OR treatment*)):ti

KQ	Set #	Concept	Strategy
KQ 3 (stimulant use disorder medications) (cont.)	#3	Intervention: Named drugs and drug classes	'opiate agonist'/exp/dd_dt OR 'opiate antagonist'/exp/dd_dt OR agonist/exp/dd_dt OR 'GABAergic receptor affecting agent'/exp/dd_dt OR '4 aminobutyric acid receptor stimulating agent'/exp/dd_dt OR 'antidepressant agent'/exp/dd_dt OR 'atypical antipsychotic agent'/exp/dd_dt OR 'anticonvulsive agent'/exp/dd_dt OR 'amino acid receptor affecting agent'/exp/dd_dt OR 'serotonin uptake inhibitor'/exp/dd_dt OR 'disulfiram'/exp OR 'topiramate'/exp OR 'doxazosin'/exp OR 'vigabatrin'/exp OR 'galantamine'/exp OR 'desipramine'/exp OR amineptine 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 Mirtazapine OR Tetrahydrocannabinol OR Lofexidine OR Lucemyra OR Dronabinol OR Modafinil OR Baclofen OR gabapentin OR Buprenorphine OR methadone OR Naltrexone OR Ondansetron OR Aripiprazole OR methylphenidate OR Dextroamphetamine OR dexamphetamine OR Varenicline OR riluzole OR pexacerfont OR Flumazenil OR hydroxyzine OR doxazosin OR uroprost OR vigabatrin OR galantamine OR desipramine OR galanthamine
	#4	Combine sets	#1 AND (#2 OR #3)
	#5	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table
KQ 4 (cannabis use disorder medications)	#1	Population: Cannabis use disorder	'cannabis addiction'/exp OR 'cannabis use disorder'/exp OR (('addiction'/exp OR 'drug abuse'/exp OR 'drug dependence'/exp OR 'drug withdrawal'/de OR 'withdrawal syndrome'/de) AND ('cannabis'/exp OR 'cannabis use'/exp OR 'medical cannabis'/exp)) OR ((cannabis* OR hashish OR marihuana OR marijuana) NEAR/3 (abuse* OR addict* OR depend* OR discontinu* OR disorder* OR misuse OR use* OR withdraw*)):ti,ab
	#2	Intervention: Broad drug therapy terms	'drug therapy'/exp OR 'drug therapy'/lnk OR 'drug combination'/exp OR 'drug combination'/lnk OR 'drug administration'/exp OR 'drug administration'/lnk OR 'drug comparison'/exp OR 'drug comparison'/lnk OR 'drugs used in the treatment of addiction'/exp OR 'drug dependence treatment'/de OR 'maintenance drug dose'/de OR 'maintenance therapy'/de OR pharmacotherap*:ti OR maintenance:ti OR (((medicine* OR medicat* OR drug* OR prescription*) NEAR/3 (therap* OR treat OR treats OR treating OR treatment*)):ti)
	#3	Intervention: Named drugs and drug classes	'acetylcysteine'/exp OR 'allosteric modulator'/exp OR 'amfebutamone'/exp OR 'cannabinoid receptor affecting agent'/exp OR 'fatty acid amidase'/de OR 'fatty acid amidase inhibitor'/exp OR 'valproate semisodium'/exp OR 'baclofen'/exp OR 'mirtazapine'/exp OR 'entacapone'/exp OR ('allosteric modulator*' OR ambien OR atomoxetine OR bupropion OR buproprion OR buspar OR buspirone OR clonidine OR clozapine OR divalproex OR dronabinol OR faah* OR ('fatty acid' NEXT/1 (amidase OR amide) NEXT/1 (hydrolase OR inhibit*)) OR escitalopram OR fluoxetine OR gabapentin OR galantamine OR guanfacine OR horizant OR lithium OR lofexidine OR nabilone OR nabiximols OR 'n acetylcysteine' OR nefazodone OR neurontin OR oxytocin OR progesterone OR topiramate OR venlafaxine OR vilazodone OR ziprasidone OR zolpidem OR baclofen OR mirtazapine OR entacapone):ti,ab
	#4	Combine sets	#1 AND (#2 OR #3)
	#5	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table

KQ	Set #	Concept	Strategy
KQ 5 (cannabis disorder addiction-focused psychotherapies OR psychosocial interventions)	#1	Population: Cannabis use disorder	'cannabis addiction'/exp OR 'cannabis use disorder'/exp OR (('addiction'/exp OR 'drug abuse'/exp OR 'drug dependence'/exp) AND ('cannabis'/exp OR 'cannabis use'/exp OR 'medical cannabis'/exp)) OR ((cannabis* OR hashish OR marihuana OR marijuana) NEAR/3 (abuse* OR addict* OR depend* OR disorder* OR misuse OR use*)):ti,ab
	#2	Intervention: Addiction focused psychotherapies OR psychosocial interventions	'community based rehabilitation'/exp OR counseling/exp OR 'motivation'/exp OR psychotherapy/exp OR 'social support'/exp OR 'support group'/exp OR 'social competence'/exp OR (((behav* OR cognitiv* OR couple* OR famil* OR group* OR motivation* OR psychoso*) NEAR/2 (counsel* OR management OR therap*)) OR (cognitiv* NEAR/2 (behav* OR therap*)) OR counsel* OR ((community OR mutual) NEAR/2 (group* OR help OR support)) OR 'community reinforcement' OR 'contingency management' OR (famil* NEAR/2 (therap* OR train*)) OR motivational OR (motivation* NEAR/2 interview*) OR psychoso* OR psychoeducat* OR (psychodynamic NEAR/2 therap*) OR psychotherap* OR 'self help' OR (support* NEAR/2 group*) OR (twelve NEXT/1 step) OR '12 step' OR ((social OR interpersonal) NEAR/3 (skill* OR train*))):ti,ab
	#3	Combine sets	#1 AND #2
	#4	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table
KQ 6 (benzodiazepine withdrawal)	#1	Population: benzodiazepine use disorder OR sedative, hypnotic, OR anxiolytic use disorder, OR withdrawal	'benzodiazepine dependence'/exp OR (('hypnotic sedative agent'/exp OR 'sedative agent'/exp OR 'barbituric acid derivative'/exp OR 'benzodiazepine derivative'/exp OR 'benzodiazepine receptor stimulating agent'/exp OR 'anxiolytic agent'/exp OR 'central depressant agent'/de OR 'anticonvulsive agent'/exp OR '4 aminobutyric acid receptor stimulating agent'/exp) AND ('substance abuse'/exp/mj OR 'drug dependence'/mj OR 'drug abuse pattern'/exp OR 'drug misuse'/exp OR 'drug seeking behavior'/exp OR 'multiple drug abuse'/exp OR 'withdrawal syndrome'/de OR 'drug craving'/exp OR 'withdrawal seizure'/de OR 'addiction'/mj OR 'addiction medicine'/exp OR 'treatment withdrawal'/exp/mj OR 'drug withdrawal'/exp/mj)) OR ((Hypnotic* OR sedative* OR alprazolam OR Benzodiazepine* OR barbiturate* OR Butalbital OR chlordiazepoxide OR clonazepam OR Librium OR klonopin OR lorazepam OR Fiorina OR Amytal OR Nembutal OR Seconal OR Phenobarbital OR barbs OR Ativan OR Halcion OR Valium OR Xanax OR downers OR Ambien OR zolpidem OR Sonata OR zaleplon OR Lunesta OR eszopiclone OR diazepam OR anoxiolytic OR Rohypnol OR 'chloral hydrate' OR glutethimide OR methaqualone OR Quaalude* OR meprobamate OR depressant* OR flurazepam OR dalmane OR quazepam OR doral OR triazolam OR estazolam OR prosom OR temazepam OR restoril OR trazodone OR oleptro OR desyrel OR amitriptyline OR elavil OR doxepin OR sinequan OR ramelteon OR rozerem OR mirtazapine OR remeron OR quetiapine OR Seroquel OR prazosin OR minipress OR melatonin OR 'z drug' OR 'z drugs') NEAR/3 (dependen* OR abuse OR misuse OR addict* OR disorder* OR user OR users OR withdraw* OR detoxif* OR taper* OR discontinu* OR substitut*)):ti,ab
	#2	Intervention: Broad drug therapy terms	'drug therapy'/exp OR 'drug therapy'/lnk OR 'drug combination'/exp OR 'drug combination'/lnk OR 'drug administration'/exp OR 'drug administration'/lnk OR 'drug comparison'/exp OR 'drug comparison'/lnk OR 'drugs used in the treatment of addiction'/exp OR 'drug dependence treatment'/de OR 'maintenance drug dose'/de OR 'maintenance therapy'/de OR pharmacotherap*:ti OR maintenance:ti OR ((medicine* OR medicat* OR drug* OR prescription*) NEAR/3 (therap* OR treat OR treats OR treating OR treatment*)):ti

KQ	Set #	Concept	Strategy
KQ 6 (benzodiazepine withdrawal) (cont.)	#3	Intervention: Named drugs and drug classes	'carbamazepine'/exp OR 'valproic acid'/exp OR 'valproate semisodium'/exp OR 'propranolol'/exp OR 'clonidine'/exp OR 'hydroxyzine'/exp OR 'diphenhydramine'/exp OR 'gabapentin'/exp OR 'promethazine'/exp OR 'metoclopramide'/exp OR 'antacid agent'/exp OR 'paracetamol'/exp OR 'nonsteroid antiinflammatory agent'/exp OR 'pregabalin'/exp OR 'captodiamine'/exp OR 'paroxetine'/exp OR 'tricyclic antidepressant agent'/exp OR 'alpidem'/exp OR 'buspirone'/exp OR 'flumazenil'/exp OR 'benzodiazepine receptor affecting agent'/exp OR 'diazepam'/exp OR 'clonazepam'/exp OR 'fluoxetine'/exp OR 'sertraline'/exp OR 'antidepressant agent'/exp OR 'serotonin receptor affecting agent'/exp OR 'ondansetron'/exp OR 'beta adrenergic receptor blocking agent'/exp OR Carbamazepine OR 'valproic acid' OR 'Divalproex sodium' OR 'valproate semisodium' OR Propranolol OR Clonidine OR Hydroxyzine OR Diphenhydramine OR Gabapentin OR Promethazine OR Metoclopramide OR (Calcium NEXT/1 carbonate) OR Mylanta OR (milk NEXT/1 magnesia) OR Acetaminophen OR paracetamol OR Ibuprofen OR 'valporate sodium' OR pregabalin OR captodiame OR captodiamine OR paroxetine OR antidepressant* OR (anti NEXT/1 depressant*) OR alipdem OR busipirone OR flumazenil OR buspirone OR flumazenil OR diazepam OR clonazepam OR fluoxetine OR Prozac OR sertraline OR ondansetron OR (beta NEXT/4 block*) OR (adrenergic NEXT/4 block*)
	#4	Combine sets	#1 AND (#2 OR #3)
	#5	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table
KQ 8 (strategies used for promoting active involvement in available mutual help programs)	#1	Population: SUD	'addiction'/mj OR 'drug abuse'/exp OR 'drug dependence'/exp OR 'alcoholism'/exp OR 'alcohol abuse'/exp OR 'opioid use disorder'/exp OR 'substance abuse'/exp OR 'cannabis use'/exp OR 'substance use'/de OR 'withdrawal syndrome'/exp OR 'inhalant abuse'/exp OR (((alcohol* OR amphetamine* OR benzodiazepine* OR cannabis OR cocaine OR drug* OR ecstasy OR heroin OR inhalant* OR marijuana OR mdma OR methadone OR narcotic* OR opiate* OR opioid* OR opium OR psychostimulant* OR solvent* OR substance* OR polydrug* OR poly-drug*) NEAR/3 (abstain* OR abstinen* OR abus* OR addict* OR behavi* OR depend* OR disorder* OR habit* OR illegal* OR illicit* OR intoxica* OR misus* OR use OR user* OR usin* OR utilis* OR utiliz* OR withdraw*)):ti, ab)
	#2	Intervention: Named facilitation strategies	((12 OR twelve) NEXT/2 'step facilitation') OR 'TSF' OR ((systematic NEXT/2 encouragement) AND (community NEXT/2 access)) OR 'SECA' OR (('making AA' OR 'making alcoholics') NEXT/2 (easier OR eazier)) OR 'MAAEZ' OR 'project match' OR (('peer alternatives') NEXT/2 addiction) OR (('stimulant abuser groups' NEXT/2 engag*) AND ((12 OR twelve) NEXT/1 step)) OR 'stage 12' OR 'stage-12' OR 'network support' OR (enhance* NEAR/3 referral*)
	#3	Intervention: Mutual help programs	'group therapy'/exp OR 'support group'/exp OR 'alcohol rehabilitation program'/exp OR 'alcoholics anonymous'/exp OR 'narcotics anonymous'/exp OR 'community based rehabilitation'/exp OR ((group OR peer*) NEAR/2 (counseling OR therap* OR support*)):ti,ab OR ((alcohol* OR narcotic* OR cocaine*) NEXT/1 anonymous) OR 'al anon' OR 'al-anon' OR (self NEXT/1 help):ti,ab OR ((mutual OR community OR peer) NEAR/1 (help OR group* OR support* OR aid OR led OR assist*)):ti,ab OR '12 step' OR (twelve NEXT/1 step) OR 'women for sobriety' OR 'self-management and recovery training' OR 'smart recovery' OR 'lifering' OR 'secular organizations for sobriety' OR 'moderation management' OR meetings:ti,ab

KQ	Set #	Concept	Strategy
KQ 8 (strategies used for promoting active involvement in available mutual help programs) (cont.)	#4	Intervention: General terms for treatment facilitation/referral	'patient compliance'/de OR 'patient attendance'/exp OR 'patient referral'/exp OR buddy OR buddies OR peer:ti OR peers:ti OR facilitat*:ti OR adher*:ti OR attend*:ti OR engag*:ti OR involv*:ti OR accept*:ti OR commit*:ti OR utiliz*:ti OR utilis*:ti OR refer:ti OR referral:ti OR ((treatment* OR therap*) NEAR/2 (adher* OR utilis* OR utiliz* OR refer* OR accept* OR commit* OR engag* OR involv*)):ti, ab
	#5	Combine sets – specific facilitation strategies	#1 AND #2
	#6	Combine sets – backup search to identify studies on promoting involvement in mutual help programs that do not mention a specific strategy	#1 AND #3 AND #4
	#7	Combine sets	#5 OR #6
	#8	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table
KQ 9 (SUD screening)	#1	Population: SUD	'addiction'/mj OR 'drug abuse'/exp/mj OR 'drug dependence'/exp/mj OR 'opioid use disorder'/exp/mj OR 'substance abuse'/exp/mj OR 'cannabis use'/exp/mj OR 'substance use'/mj OR 'withdrawal syndrome'/exp/mj OR 'inhalant abuse'/exp/mj OR ((amphetamine* OR benzodiazepine* OR cannabis OR cocaine OR drug* OR ecstasy OR heroin OR inhalant* OR marijuana OR mdma OR methadone OR narcotic* OR opiate* OR opioid* OR opium OR psychostimulant* OR solvent* OR substance*) NEAR/3 (abstain* OR abstinen* OR abus* OR addict* OR behavi* OR depend* OR disorder* OR habit* OR illegal* OR illicit* OR intoxica* OR misus* OR use OR user* OR usin* OR utilis* OR utiliz* OR withdraw*)): ti
	#2	Intervention: Mass screening	'mass screening'/mj OR 'screening test'/exp/mj OR screening/mj OR 'drug screening'/exp/mj OR (screen* OR question* OR form OR forms OR tool* OR assessment* OR scale* OR instrument* OR survey* OR inventory OR inventories OR score):ti
	#3	Intervention: Named screening tools	'cannabis abuse screening test' OR 'current opioid misuse measure' OR 'drug abuse screening test' OR 'emergency medicine providers clinician assessment questionnaire' OR 'emergency provider impression data collection form' OR 'opioid risk tool' OR 'readiness to change questionnaire' OR 'screener and opioid assessment for patients with pain' OR 'substance abuse screening inventory' OR (4p NEXT/1 s) OR ((form OR forms OR tool* OR test* OR screen* OR question* OR scale* OR survey*) NEAR/5 (assist OR cast OR crafft OR dast* OR dhq* OR dudit OR dus OR nida OR nmassist OR rcq* OR sds OR 'sip ad' OR 'ssi sa' OR soapp* OR 'surp-p' OR taps OR tics OR uncope OR widus OR 'wayne indirect')):ti,ab
	#4	Combine sets	#1 AND (#2 OR #3)
	#5	Apply limits, remove unwanted populations and publication types	See strategies at the end of the table
	#6	limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table

KQ	Set #	Concept	Strategy
KQ 9 (SUD screening) (cont.)	#7	Limit to observational study type designs	#5 AND ('cohort analysis' OR 'comparative study'/exp OR 'controlled study'/exp OR 'evaluation study'/de OR 'longitudinal study'/de OR 'major clinical study'/de OR 'observational study'/de OR 'prospective study'/de OR 'treatment outcome'/de OR ('between groups' OR 'case control*' OR cohort* OR comparison OR comparative OR 'control group*' OR 'controlled study' OR 'controlled trial' OR 'cross over' OR crossover OR 'double blind' OR 'double blinded' OR longitudinal OR 'matched controls' OR (observational NEXT/3 study) OR placebo* OR prospective OR random* OR sham):ti,ab OR (versus OR vs):ti)
	#8	Combine sets	#6 OR #7
KQ 10 (telehealth and virtual health modalities); KQ 11 (technology-based interventions)	#1	Population: SUD	'addiction'/mj OR 'drug abuse'/exp OR 'drug dependence'/exp OR 'alcoholism'/exp OR 'alcohol abuse'/exp OR 'opioid use disorder'/exp OR 'substance abuse'/exp OR 'cannabis use'/exp OR 'substance use'/de OR 'withdrawal syndrome'/exp OR 'inhalant abuse'/exp OR alcoholi*:ti,ab OR (((alcohol* OR amphetamine OR benzodiazepine* OR cannabis OR cocaine OR drug* OR ecstasy OR heroin OR inhalant* OR marijuana OR mdma OR methadone OR narcotic* OR opiate* OR opioid* OR opium OR psychostimulant* OR solvent* OR substance*) NEAR/3 (abstain* OR abstinence* OR abus* OR addict* OR behavi* OR depend* OR disorder* OR habit* OR illegal* OR illicit* OR intoxica* OR misus* OR use OR user* OR usin* OR utilis* OR withdraw*)):ti,ab)
	#2	Intervention: Telehealth (including mental health terms) (KQ 10)	'online monitoring'/exp OR 'teleconsultation'/exp OR 'telehealth'/exp OR 'telemedicine'/exp OR 'telemonitoring'/exp OR 'technology assisted health coaching'/exp OR 'videoconferencing'/exp OR 'e health*':ti,ab,de OR ehealth*:ti,ab,de OR 'm health*':ti,ab,de OR mhealth*:ti,ab,de OR telehealth:ti,ab,de OR telemed*:ti,ab,de OR telepsych*:ti,ab,de OR telebehavior*:ti,ab,de OR telemental*:ti,ab,de OR telerehab*:ti,ab,de OR telemonitor*:ti,ab,de OR teleconsult*:ti,ab,de OR ((tele NEXT/1 (health OR medicine OR psychiatr* OR psycholog* OR monitor*)):ti,ab,de) OR telephone*:ti,ab,de OR phone*:ti,ab,de OR (((online OR remote* OR video* OR virtual OR digital) NEAR/2 (monitor* OR health* OR care OR medicine)):ti,ab,de) OR videoconferenc*:ti,ab,de OR ((tele NEXT/1 (health OR medicine OR psychiatry)):ti,ab,de)
	#3	Intervention: Technology based interventions (KQ 11)	'internet'/exp OR 'mobile application'/exp OR 'mobile health application'/exp OR 'social media'/exp OR 'text messaging'/exp OR 'mobile phone'/exp OR 'wireless communication'/exp OR 'virtual reality'/exp OR 'app':ti OR 'apps':ti OR web:ti OR website*:ti OR digital:ti OR cellphone*:ti,ab OR ((cell* NEXT/1 phone*):ti,ab) OR iphone:ti,ab OR internet:ti,ab OR (((mobile OR wireless OR bluetooth) NEAR/2 (health* OR device* OR application OR app OR apps)):ti,ab) OR 'social media':ti,ab OR twitter:ti,ab OR tweet:ti,ab OR ((text* NEAR/2 message*):ti,ab) OR texting:ti,ab OR facebook:ti,ab OR instagram*:ti,ab OR snapchat*:ti,ab OR laptop:ti,ab OR ((tablet NEAR/3 computer*):ti,ab) OR ipad:ti,ab OR iwatch:ti,ab OR chromebook*:ti,ab OR 'smartwatch':ti,ab OR 'apple watch':ti,ab OR 'personal digital assistant':ti,ab OR (((technology OR app OR application) NEXT/2 (based OR supported)):ti,ab) OR android:ti,ab OR helpline*:ti,ab OR smartphone*:ti,ab OR 'smart phone*':ti,ab OR alexa:ti,ab OR siri:ti,ab OR bixby:ti,ab OR reset:ti,ab OR 'reset o':ti,ab OR 'reset otm':ti,ab
	#4	Combine sets	#1 AND (#2 OR #3)
	#5	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table

KQ	Set #	Concept	Strategy
KQ 12 (addiction-focused mindfulness-based therapies [e.g., ACT, mindfulness-based relapse prevention, Third Wave CBT])	#1	Population: SUD	'addiction'/mj OR 'drug abuse'/exp OR 'drug dependence'/exp OR 'alcoholism'/exp OR 'alcohol abuse'/exp OR 'opioid use disorder'/exp OR 'substance abuse'/exp OR 'cannabis use'/exp OR 'substance use'/de OR 'withdrawal syndrome'/exp OR 'inhalant abuse'/exp OR (((alcohol* OR amphetamine* OR benzodiazepine* OR cannabis OR cocaine OR drug* OR ecstasy OR heroin OR inhalant* OR marijuana OR mdma OR methadone OR narcotic* OR opiate* OR opioid* OR opium OR psychostimulant* OR solvent* OR substance* OR polydrug* OR poly-drug*) NEAR/3 (abstain* OR abstinen* OR abus* OR addict* OR behavi* OR depend* OR disorder* OR habit* OR illegal* OR illicit* OR intoxica* OR misus* OR use OR user* OR usin* OR utilis* OR utiliz* OR withdraw*)):ti,ab)
	#2	Intervention: Mindfulness based therapies	'acceptance and commitment therapy'/exp OR 'mindfulness'/exp OR 'mindfulness meditation'/exp OR 'dialectical behavior therapy'/exp OR 'meditation'/exp OR 'yoga'/exp OR mindful* OR meditat* OR mbcg OR mbsr OR mbrp OR micbt OR (acceptance NEXT/2 commitment) OR (dialectical NEXT/2 (behavior* OR behaviour*)) OR hakomi:ti,ab OR morita:ti,ab OR (mode NEXT/2 deactivat*) OR (third NEXT/2 wave) OR yoga OR (breathing NEAR/2 (deep OR exercise*))
	#3	Combine sets	#1 AND #2
	#4	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table
Limits and hedges applied to each search strategy		Limit to results added to the database between January 1, 2015, and June 30, 2020	[1-1-2015]/sd NOT [30-6-2020]/sd
		Limit to English language publications	AND [english]/lim
		Exclude animal and experimental studies	NOT (([animals]/lim NOT [humans]/lim) OR (animal* OR experimental OR (vitro NOT vivo) OR canine OR dog OR dogs OR mouse OR mice OR murine:ti OR pig OR pigs OR piglet* OR rabbit* OR rat OR rats OR rodent* OR sheep OR swine):ti)
		Exclude studies focusing on children	NOT ((adolescen* OR baby OR babies OR boys OR child* OR girls OR infancy OR infant* OR juvenile* OR neonat* OR newborn* OR NICU OR paediatric* OR pediatric* OR preschool* OR school OR schools OR teen* OR toddler* OR youth*):ti NOT (adult*:ti OR women:ti OR woman:ti OR pregnan*:ti))
		Remove undesired publication and study types (e.g., case reports, conferences, editorials)	NOT ('conference paper'/exp OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR ('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 ('a case' OR 'year old'):ti,ab OR 'a patient':ti OR (book OR 'conference proceeding'):pt OR ('case report' OR comment OR protocol):ti)
		Hedge to identify meta-analyses and SRs	AND ('systematic review'/de OR 'meta analysis'/de OR [cochrane review]/lim OR (systematic* NEAR/2 review*) OR metaanalysis OR metaanalyses OR (meta NEXT/1 (analysis OR analyses)) OR Cochrane:ti,ab)
		Hedge to identify RCTs	AND ('random sample'/de OR 'randomized controlled trial'/de OR randomization/de OR (random* OR RCT):ti,ab)

B. PsycINFO in Ovid Syntax (all KQs)

KQ	Set #	Concept	Strategy
KQ 1 (OUD medications); KQ 2 (OUD medication w/out psychological therapy); KQ 7 (opioid withdrawal)	#1	Population: OUD	exp 'opioid use disorder'/ OR ((exp drug abuse/ OR exp drug dependency/ OR exp drug addiction/ OR exp addiction/ OR exp drug withdrawal/) AND (exp narcotic drugs/ OR exp analgesic drugs/)) OR ((analgesic* OR codeine OR fentanyl OR heroin OR hydrocodone OR methadone OR morphine OR narcotic* OR opiate* OR opioid* OR opium OR oxycodone OR oxycontin OR percocet) ADJ3 (abuse OR addict* OR dependen* OR disorder* OR withdraw* OR detoxif*)).ti,ab.
	#2	Intervention: Broad drug therapy terms	exp Drug Therapy/ OR exp Maintenance Therapy/ OR medication-assisted treatment/ OR pharmacotherap*.ti. OR ((medicine* OR medicat* OR drug*) ADJ3 (therap* OR treat OR treatment*)).ti. OR maintenance.ti.
	#3	Intervention: Named drugs and drug classes	exp narcotic agonists/ OR exp narcotic antagonists/ OR exp adrenergic drugs/ OR exp Clonidine/ OR exp gabapentin/ OR exp Venlafaxine/ OR exp Haloperidol/ OR (alpha ADJ3 adrenergic) OR acetylmethadol OR buprenorphine OR clonidine OR guanabenz OR guanfacine OR LAAM OR levacetylmethadol OR lofexidine OR methadone OR naloxone OR naltrexone OR narcan* OR gabapentin OR hydromorphone OR tramadol OR tizanidine OR venlafaxine OR mirtazapine OR haloperidol
	#4	Combine concepts	1 AND (2 OR 3)
	#5	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table
KQ 3 (stimulant use disorder medications)	#1	Population: Stimulant/ amphetamine/ cocaine	((exp drug abuse/ OR exp drug dependency/ OR exp polydrug abuse/ OR addiction/ OR exp drug addiction/ OR exp drug withdrawal/) AND (exp Amphetamine/ OR exp Cocaine/ OR exp Crack Cocaine/ OR exp CNS Stimulating Drugs/)) OR ((amphetamine* OR atomoxetine OR cocaine OR lisdexamfetamine OR methamphetamine* OR methylphenidate OR dextroamphetamine OR dexamphetamine OR dexmethylphenidate OR Dexedrine OR Adderall OR mydayis OR stimulant* OR 'meth' OR analeptic* OR ecstasy OR MDMA OR oxymetazoline OR pseudoephedrine OR phenylephrine) ADJ3 (abuse OR misus* OR addict* OR detox* OR disorder* OR user OR users OR dependen* OR withdraw*)).ti,ab.
	#2	Intervention: Broad drug therapy terms	exp Drug Therapy/ OR exp Maintenance Therapy/ OR medication-assisted treatment/ OR pharmacotherap*.ti. OR ((medicine* OR medicat* OR drug* OR prescription*) ADJ3 (therap* OR treat OR treatment*)).ti. OR maintenance.ti.
	#3	Intervention: Named drugs and drug classes	Exp disulfiram/ OR exp adrenergic drugs/ OR exp narcotic agonists/ OR exp Dopamine Agonists/ OR exp Serotonin Agonists/ OR exp Benzodiazepine Agonists/ OR exp Narcotic Agonists/ OR exp galanthamine/ OR exp desipramine/ OR exp antidepressant drugs/ OR amineptine 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 Mirtazapine OR Tetrahydrocannabinol OR Lofexidine OR Lucemyra OR Dronabinol OR Modafinil OR Baclofen OR gabapentin OR Buprenorphine OR methadone OR Naltrexone OR Ondansetron OR Aripiprazole OR methylphenidate OR Dextroamphetamine OR dexamphetamine OR Varenicline OR riluzole OR pexacerfont OR Flumazenil OR hydroxyzine OR doxazosin OR uroprost OR vigabatrin OR galantamine OR galanthamine OR desipramine
	#4	Combine sets	1 AND (2 OR 3)
	#5	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table

KQ	Set #	Concept	Strategy
KQ 4 (cannabis use disorder medications)	#1	Population: Cannabis use disorder	exp "cannabis use disorder"/ OR ((exp drug abuse/ OR exp drug dependency/ OR addiction/ OR exp drug withdrawal/) AND exp cannabis/) OR ((cannabis* OR hashish OR marihuana OR marijuana) ADJ3 (abuse* OR addict* OR depend* OR discontinu* OR disorder* OR misuse OR use* OR withdraw*)).ti,ab.
	#2	Intervention: Broad drug therapy terms	exp Drug Therapy/ OR exp Maintenance Therapy/ OR medication-assisted treatment/ OR pharmacotherap*.ti. OR ((medicine* OR medicat* OR drug* OR prescription*) ADJ3 (therap* OR treat OR treatment*)).ti. OR maintenance.ti.
	#3	Intervention: Named drugs and drug classes	exp Cannabinoids/ OR Exp baclofen'/ OR ((allosteric ADJ2 modulator*) OR acetylcysteine OR ambien OR amfebutamone OR atomoxetine OR bupropion OR buproprion OR buspar OR buspirone OR (cannabinoid* ADJ5 (agent* OR agonist* OR antagonist* OR receptor*)) OR clonidine OR clozapine OR divalproex OR dronabinol OR faah* OR 'fatty acid amidase inhibit*' OR 'fatty acid amide hydrolase' OR escitalopram OR fluoxetine OR gabapentin OR galantamine OR guanfacine OR horizant OR lithium OR lofexidine OR nabilone OR nabiximols OR 'n acetylcysteine' OR nefazodone OR neurontin OR oxytocin OR progesterone OR topiramate OR (valproate ADJ2 semisodium) OR venlafaxine OR vilazodone OR ziprasidone OR zolpidem OR OR baclofen OR mirtazapine OR entacapone).ti,ab.
	#4	Combine sets	1 AND (2 OR 3)
	#5	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table
KQ 5 (cannabis disorder addiction-focused psychotherapies OR psychosocial interventions)	#1	Population: Cannabis use disorder	exp "cannabis use disorder"/ OR ((exp drug abuse/ OR exp drug dependency/ OR addiction/ OR exp drug withdrawal/) AND exp cannabis/) OR((cannabis* OR hashish OR marihuana OR marijuana) ADJ3 (abuse* OR addict* OR depend* OR disorder* OR misuse OR use*)).ti,ab.
	#2	Intervention: Addiction focused psychotherapies OR psychosocial interventions	exp counseling/ OR exp motivation/ OR exp motivation training/ OR exp psychotherapy/ OR exp rehabilitation/ OR exp social support/ OR exp support groups/ OR exp social skills/ OR exp social skills training/ OR (((behav* OR cognitiv* OR couple* OR famil* OR group* OR motivation* OR psychoso*) ADJ2 (counsel* OR management OR therap*)) OR (cognitiv* ADJ2 (behav* OR therap*)) OR counsel* OR ((community OR mutual) ADJ2 (group* OR help OR support)) OR "community reinforcement" OR "contingency management" OR (famil* ADJ2 (therap* OR train*)) OR motivational OR (motivation* ADJ2 interview*) OR psychoso* OR psychoeducat* OR (psychodynamic ADJ2 therap*) OR psychotherap* OR "self help" OR (support ADJ2 group*) OR (twelve ADJ1 step) OR "12 step" OR ((social OR interpersonal) ADJ3 (skill* OR train*))).ti,ab.
	#3	Combine sets	1 AND 2
	#4	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table

KQ	Set #	Concept	Strategy
KQ 6 (benzodiazepine withdrawal)	#1	Population: benzodiazepine use disorder OR sedative, hypnotic, OR anxiolytic use disorder	(exp Benzodiazepines/ OR exp sedatives/ OR exp Hypnotic Drugs/ OR exp gamma aminobutyric acid agonists/ OR exp tranquilizing drugs/ OR exp Anticonvulsive Drugs/) AND ('substance use disorder'/ OR exp drug abuse/ OR exp drug dependency/ OR exp drug addiction/ OR exp addiction/ OR exp drug withdrawal/ OR exp detoxification/) OR ((Hypnotic* OR sedative* OR alprazolam OR Benzodiazepine* OR barbiturate* OR Butalbital OR chlordiazepoxide OR clonazepam OR Librium OR klonopin OR lorazepam OR Fiorina OR Amytal OR Nembutal OR Seconal OR Phenobarbital OR barbs OR Ativan OR Halcion OR Valium OR Xanax OR downers OR Ambien OR zolpidem OR Sonata OR zaleplon OR Lunesta OR eszopiclone OR diazepam OR anoxiolytic OR Rohypnol OR 'chloral hydrate' OR glutethimide OR methaqualone OR Quaalude* OR meprobamate OR depressant* OR flurazepam OR dalmane OR quazepam OR doral OR triazolam OR estazolam OR prosom OR temazepam OR restoril OR trazodone OR oleptro OR desyrel OR amitriptyline OR elavil OR doxepin OR sinequan OR ramelteon OR rozerem OR mirtazapine OR remeron OR quetiapine OR Seroquel OR prazosin OR minipress OR melatonin OR 'z drug' OR 'z drugs') ADJ3 (dependen* OR abuse OR misuse OR addict* OR disorder* OR user OR users OR withdraw* OR detoxif* OR taper* OR discontinu* OR substitut*)).ti,ab.
	#2	Intervention: Broad drug therapy terms	exp Drug Therapy/ OR exp Maintenance Therapy/ OR medication-assisted treatment/ OR pharmacotherap*.ti. OR ((medicine* OR medicat* OR drug* OR prescription*) ADJ3 (therap* OR treat OR treats OR treating OR treatment*)).ti. OR maintenance.ti.
	#3	Intervention: Named drugs and drug classes	exp carbamazepine/ OR exp Valproic Acid/ OR exp propranolol/ OR exp clonidine/ OR exp hydroxyzine/ OR exp diphenhydramine/ OR exp gabapentin/ OR exp Promethazine/ OR exp anti inflammatory drugs/ OR exp pregabalin/ OR exp paroxetine/ OR exp Antidepressant Drugs/ OR 'alpidem'/exp OR exp buspirone/ OR exp benzodiazepine agonists/ OR exp benzodiazepine antagonists/ OR exp diazepam/ OR exp clonazepam/ OR exp fluoxetine'/ OR exp sertraline/ OR exp Adrenergic Blocking Drugs/ OR (Carbamazepine OR 'valproic acid' OR 'Divalproex sodium' OR 'valproate semisodium' OR propranolol OR Clonidine OR Hydroxyzine OR Diphenhydramine OR Gabapentin OR Promethazine OR Metoclopramide OR (Calcium ADJ1 carbonate) OR Mylanta OR (milk ADJ2 magnesia) OR Acetaminophen OR paracetamol OR Ibuprofen OR 'valporate sodium' OR pregabalin OR captodiame OR captodiamine OR paroxetine OR antidepressant* OR (anti ADJ1 depressant*) OR alipdem OR busipirone OR flumazenil OR buspirone OR flumazenil OR diazepam OR clonazepam OR fluoxetine OR Prozac OR sertraline OR ondansetron OR (beta ADJ4 block*) OR (adrenergic ADJ/4 block*)).ti,ab.
	#4	Combine sets	1 AND (2 OR 3)
	#5	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table

KQ	Set #	Concept	Strategy
KQ 8 (strategies used for promoting active involvement in available mutual help programs)	#1	Population: SUD	exp drug addiction/ OR exp drug abuse/ OR exp drug overdoses/ OR exp drug seeking/ OR exp intravenous drug usage/ OR exp 'substance use disorder'/ OR exp alcohol abuse/ OR exp Alcoholism/ OR exp addiction treatment/ OR (((alcohol* OR amphetamine* OR benzodiazepine* OR cannabis OR cocaine OR drug* OR ecstasy OR heroin OR inhalant* OR marijuana OR mdma OR methadone OR narcotic* OR opiate* OR opioid* OR opium OR psychostimulant* OR solvent* OR substance*) ADJ3 (abstain* OR abstinen** OR abus* OR addict* OR behavi* OR depend* OR disorder* OR habit* OR illegal* OR illicit* OR intoxica* OR misus* OR user* OR usin* OR utilis* OR utiliz* OR withdraw*)).ti,ab.)
	#2	Intervention: Named facilitation strategies	(twelve ADJ2 'step facilitation') OR '12 step facilitation' OR '12-step facilitation' OR 'TSF' OR ((systematic ADJ2 encouragement) AND (community ADJ2 access)) OR 'SECA' OR (('making AA' OR 'making alcoholics') ADJ2 (easier OR eazier)) OR 'MAAEZ' OR 'project match' OR (('peer alternatives') ADJ2 addiction) OR (('stimulant abuser groups' ADJ2 engag*) AND ('12 step' OR '12-step' OR 'twelve-step' OR 'twelve step')) OR 'stage 12' OR 'stage-12' OR 'network support' OR (enhance* ADJ3 referral*)
	#3	Intervention: Mutual help programs	exp Group Psychotherapy/ OR exp support groups/ OR exp alcoholics anonymous/ OR exp twelve step programs/ OR ((group OR peer*) ADJ2 (counseling OR therap* OR support*)).ti,ab. OR ((alcohol* OR narcotic* OR cocaine*) ADJ1 anonymous).mp. OR 'al anon'.mp. OR 'al-anon'.mp. OR (self ADJ1 help).mp. OR ((mutual OR community OR peer) ADJ2 (help OR group* OR support OR aid OR led OR assist*)).ti,ab. OR '12 step' OR (twelve ADJ1 step) OR 'women for sobriety' OR 'self-management and recovery training' OR 'smart recovery' OR 'lifering' OR 'secular organizations for sobriety' OR 'moderation management' OR meetings.ti,ab.
	#4	General terms for treatment facilitation/referral	exp Treatment Compliance/ OR exp client treatment matching/ OR exp Self-Referral/ OR exp Professional Referral/ OR buddy OR buddies OR peer.ti. OR peers.ti. OR facilitat*.ti. OR adher*.ti. OR attend*.ti. OR engag*.ti. OR involv*.ti. OR accept*.ti. OR commit*.ti. OR utiliz*.ti. OR utilis*.ti. OR refer.ti. OR referral.ti. OR ((treatment* OR therap*) ADJ2 (adher* OR utilis* OR utiliz* OR refer* OR accept* OR commit* OR engag* OR involv*)).ti,ab.
	#5	Combine sets – specific strategies	1 AND 2
	#6	Combine sets – backup search to identify studies on promoting involvement in mutual help programs that do not mention a specific strategy	1 AND 3 AND 4
	#7	Combine sets	5 OR 6
	#8	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table

KQ	Set #	Concept	Strategy
KQ 9 (SUD screening)	#1	Population: SUD	exp *drug addiction/ OR exp *drug abuse/ OR exp *drug overdoses/ OR exp *drug seeking/ OR exp *intravenous drug usage/ OR exp *'substance use disorder'/ OR exp *addiction treatment/ OR ((amphetamine* OR benzodiazepine* OR cannabis OR cocaine OR drug* OR ecstasy OR heroin OR inhalant* OR marijuana OR mdma OR methadone OR narcotic* OR opiate* OR opioid* OR opium OR psychostimulant* OR solvent* OR substance*) ADJ3 (abstain* OR abstinen* OR abus* OR addict* OR behavi* OR depend* OR disorder* OR habit* OR illegal* OR illicit* OR intoxica* OR misus* OR user* OR usin* OR utilis* OR utiliz* OR withdraw*)).ti.
	#2	Intervention: Mass screening	exp *Screening Tests/ OR exp *Drug Usage Screening/ OR exp *Screening/ OR (screen* OR question* OR form OR forms OR tool* OR assessment* OR scale* OR instrument* OR survey* OR inventory OR inventories OR score).ti.
	#3	Intervention: Named screening tools	'cannabis abuse screening test' OR 'current opioid misuse measure' OR 'drug abuse screening test' OR 'emergency medicine providers clinician assessment questionnaire' OR 'emergency provider impression data collection form' OR 'opioid risk tool' OR 'readiness to change questionnaire' OR (screener ADJ2 'opioid assessment for patients with pain') OR 'substance abuse screening inventory' OR '4ps' OR '4p's' OR ((form OR forms OR tool* OR test* OR screen* OR question* OR scale* OR survey*) ADJ5 (assist OR cast OR crafft OR dast* OR dhq* OR dudit OR dus OR nida OR nmassist OR rcq* OR sds OR 'sip ad' OR soapp* OR 'ssi sa' OR 'surp-p' OR taps OR tics OR uncope OR widus OR 'wayne indirect')).ti,ab.
	#4	Combine sets	1 AND (2 OR 3)
	#5	Apply limits, remove unwanted populations and publication types	See strategies at the end of the table
	#6	Limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table
	#7	Limit to observational study type designs	5 AND (exp Cohort Analysis/ OR exp longitudinal studies/ OR exp prospective studies/ OR exp clinical trials/ OR exp treatment outcomes/ OR ('between groups' OR 'case control*' OR cohort* OR comparison* OR comparative OR 'control group*' OR 'controlled study' OR 'controlled trial' OR 'cross over' OR crossover OR 'double blind' OR 'double blinded' OR longitudinal OR 'matched controls' OR (observational adj3 study) OR placebo* OR prospective OR random* OR sham).ti,ab. OR (versus OR vs).ti.)
	#8	Combine sets	#6 OR #7

KQ	Set #	Concept	Strategy
KQ 10 (telehealth and virtual health modalities); KQ 11 (technology-based interventions)	#1	Population: SUD	exp drug addiction/ OR exp drug abuse/ OR exp drug overdoses/ OR exp drug seeking/ OR exp intravenous drug usage/ OR exp 'substance use disorder'/ OR exp alcohol abuse/ OR exp Alcoholism/ OR exp addiction treatment/ OR alcoholi*.ti,ab. OR (((alcohol* OR amphetamine OR benzodiazepine* OR cannabis OR cocaine OR drug* OR ecstasy OR heroin OR inhalant* OR marijuana OR mdma OR methadone OR narcotic OR opiate* OR opioid* OR opium OR psychostimulant* OR solvent* OR substance) ADJ3 (abstain* OR abstinence* OR abus* OR addict* OR behavi* OR depend* OR disorder* OR habit* OR illegal* OR illicit* OR intoxica* OR misus* OR user* OR usin* OR utilis* OR withdraw*)).ti,ab.)
	#2	Intervention: Telehealth (including mental health terms) (KQ10)	exp telemedicine/ OR exp computer assisted therapy/ OR exp electronic health services/ OR exp videoconferencing/ OR exp video-based interventions/ OR exp mobile health/ OR exp online therapy/ OR exp telepsychiatry/ OR exp telepsychology/ OR (('e health' OR ehealth* OR 'm health' OR mhealth* OR telehealth OR telemed* OR telepsych* OR telemonitor* OR telerehab* OR teleconsult* OR telemental* OR telebehavior* OR (tele ADJ1 (health OR medicine OR psychiatr* OR psycholog* OR monitor*)) OR telephone* OR phone* OR ((online OR remote* OR video* OR virtual OR digital) ADJ2 (monitor* OR health* OR care OR medicine)) OR videoconferenc*).ti,ab.)
	#3	Intervention: Technology based interventions (KQ11)	exp 'internet'/ OR exp Mobile Applications/ OR exp Social Media/ OR exp Text Messaging/ OR exp Mobile Phones/ OR exp mobile devices/ OR exp digital technology/ OR exp Virtual Reality/ OR exp smartphones/ OR ('app' OR 'apps' OR web OR website* OR digital OR cellphone* OR (cell* ADJ1 phone*) OR iphone OR internet OR ((mobile OR wireless OR bluetooth) ADJ2 (health* OR device* OR application OR app OR apps)) OR 'social media' OR twitter OR tweet OR (text* ADJ2 message*) OR texting OR facebook OR instagram* OR snapchat* OR laptop OR (tablet ADJ3 computer*) OR ipad OR iwatch OR chromebook* OR 'smartwatch' OR 'apple watch' OR 'personal digital assistant' OR ((technology OR app OR application) ADJ2 (based OR supported)) OR android OR helpline* OR smartphone* OR 'smart phone' OR 'smart phones' OR alexa OR siri OR bixby OR reset OR 'reset o' OR 'reset otm').ti,ab.
	#4	Combine sets	1 AND (2 OR 3)
	#5	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table

KQ	Set #	Concept	Strategy
KQ 12 (addiction-focused mindfulness-based therapies [e.g., ACT, mindfulness-based relapse prevention, Third Wave CBT])	#1	Population: SUD	exp drug addiction/ OR exp drug abuse/ OR exp drug overdoses/ OR exp drug seeking/ OR exp intravenous drug usage/ OR exp 'substance use disorder'/ OR exp alcohol abuse/ OR exp Alcoholism/ OR exp addiction treatment/ OR (((alcohol* OR amphetamine* OR benzodiazepine* OR cannabis OR cocaine OR drug* OR ecstasy OR heroin OR inhalant* OR marijuana OR mdma OR methadone OR narcotic* OR opiate* OR opioid* OR opium OR psychostimulant* OR solvent* OR substance*) ADJ3 (abstain* OR abstinen* OR abus* OR addict* OR behavi* OR depend* OR disorder* OR habit* OR illegal* OR illicit* OR intoxica* OR misus* OR user* OR usin* OR utilis* OR utiliz* OR withdraw*)).ti,ab.)
	#2	Intervention: Mindfulness based therapies	exp 'Acceptance and Commitment Therapy'/ OR exp mindfulness/ OR exp dialectical behavior therapy/ OR exp meditation/ OR exp mindfulness-based interventions/ OR exp morita therapy/ OR exp yoga/ OR mindful* OR meditat* OR mbcg OR mbsr OR micbt OR (acceptance ADJ2 commitment) OR (dialectical ADJ2 (behavior* OR behaviour*)) OR hakomi.ti,ab. OR morita.ti,ab. OR (mode ADJ2 deactivat*) OR (third ADJ2 wave) OR yoga OR (breathing ADJ2 (deep OR exercise*))
	#3	Combine sets	1 AND 2
	#4	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table
Limits and hedges applied to each search strategy		Limit to results added to the database between January 1, 2015, and June 30, 2020	limit to up=20150101-20200630
		Limit to English language publications	AND English.lg.
		Exclude animal and experimental studies	NOT (animal* OR experimental OR (vitro NOT vivo) OR canine OR dog OR dogs OR mouse OR mice OR murine OR pig OR pigs OR piglet* OR rabbit* OR rat OR rats OR rodent* OR sheep OR swine).ti.
		Exclude studies focusing on children	NOT ((adolescen* OR baby OR babies OR boys OR child* OR girls OR infancy OR infant* OR juvenile* OR neonat* OR newborn* OR NICU OR paediatric* OR pediatric* OR preschool* OR school OR schools OR teen* OR toddler* OR youth*).ti. NOT (adult* OR women OR woman OR pregnan*).ti.)
		Remove undesired publication and study types (e.g., case reports, conferences, editorials)	NOT ((chapter OR 'column/opinion' OR comment OR 'comment/reply' OR dissertation OR editorial OR letter OR review-book).dt. OR (book OR encyclopedia OR 'dissertation abstract').pt. OR ('case report' OR 'a case' OR 'year-old').ti,ab. OR 'a patient'.ti.)
		Limit to meta-analyses and SRs	AND (meta analysis/ OR ('meta analysis' OR 'meta analytic' OR metaanaly* OR (systematic ADJ3 review)).ti,ab. OR systematic.ti. OR cochrane.jw.
		Limit to RCTs	AND (random sampling/ OR (random* OR RCT).ti,ab.)

C. PubMed In Process Citations

KQ	Set #	Concept	Strategy
KQ 1 (OUD medications); KQ 2 (OUD medication w/out psychological therapy); KQ 7 (opioid withdrawal)	#1	Population: OUD	(analgesic*[tiab] OR codeine[tiab] OR fentanyl[tiab] OR heroin[tiab] OR hydrocodone[tiab] OR methadone[tiab] OR morphine[tiab] OR narcotic*[tiab] OR opiate*[tiab] OR opioid*[tiab] OR opium[tiab] OR oxycodone[tiab] OR oxycontin[tiab] OR percocet[tiab]) AND (abuse[tiab] OR addict*[tiab] OR dependenc*[tiab] OR disorder*[tiab] OR intoxicat*[tiab] OR misuse[tiab] OR withdraw*[tiab] OR detoxif*[tiab])
	#2	Intervention and Comparison: Broad drug therapy terms	Maintenance[ti] OR pharmacotherap*[ti] OR ((drug[ti] OR drugs[ti] OR medication*[ti] OR prescription*[ti]) AND (administrat*[ti] OR compar*[ti] OR treatment*[ti] OR treat[ti] OR treats[ti] OR therapy[ti] OR therapeutic*[ti]))
	#3	Maintenance medications: Specific drugs and drug classes	((adrenergic[tiab] OR narcotic*[tiab] OR opioid*[tiab] OR opiate*[tiab]) AND (agonist*[tiab] OR antagonist*[tiab])) OR acetylmethadol[tiab] OR buprenorphine[tiab] OR clonidine[tiab] OR gabapentin[tiab] OR gabapentin[tiab] OR guanabenz[tiab] OR guanfacine[tiab] OR laam[tiab] OR levacetylmethadol[tiab] OR lofexidine[tiab] OR methadone[tiab] OR naloxone[tiab] OR naltrexone[tiab] OR narcan*[tiab] OR hydromorphone[tiab] OR tramadol[tiab] OR Tizanidine[tiab] OR Venlafaxine[tiab] OR Mirtazapine[tiab] OR Haloperidol[tiab]
	#4	Combine above	#1 AND (#2 OR #3)
	#5	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table
KQ 3 (stimulant use disorder medications)	#1	Population: Stimulant/ amphetamine/ cocaine	((amphetamine*[ti] OR atomoxetine[ti] OR cocaine[ti] OR lisdexamfetamine[ti] OR methamphetamine*[ti] OR methylphenidate[ti] OR dextroamphetamine[ti] OR dexamphetamine[ti] OR dexmethylphenidate[ti] OR Dexedrine[ti] OR Adderall[ti] OR mydayis[ti] OR stimulant*[ti] OR "meth"[ti] OR analeptic*[ti] OR ecstasy[ti] OR MDMA[ti] OR oxymetazoline[ti] OR pseudoephedrine[ti] OR phenylephrine[ti]) AND (abuse[ti]OR detox*[ti] OR misus*[ti] OR addict*[ti] OR disorder*[ti] OR user[ti] OR users[ti] OR withdraw*[ti] OR dependen*[ti]))
	#2	Intervention: Broad drug therapy terms	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]))
	#3	Intervention: Named drugs and drug classes	Amineptine [tiab] OR disulfiram[tiab] OR esperal[tiab] OR dicupral[tiab] OR disulfide[tiab] OR alcophobin[tiab] OR anticol[tiab] OR Antabuse[tiab] OR antabus*[tiab] OR teturam[tiab] OR topiramate[tiab] OR Topamax[tiab] OR topimax[tiab] OR Bupropion[tiab] OR Divalproex[tiab] OR Nefazodone[tiab] OR Mirtazapine[tiab] OR Tetrahydrocannabinol[tiab] OR Lofexidine[tiab] OR Lucemyra[tiab] OR Dronabinol[tiab] OR Modafinil[tiab] OR Baclofen[tiab] OR gabapentin[tiab] OR Buprenorphine[tiab] OR methadone[tiab] OR Naltrexone[tiab] OR Ondansetron[tiab] OR Aripiprazole[tiab] OR methylphenidate[tiab] OR Dextroamphetamine[tiab] OR dexamphetamine OR Varenicline[tiab] OR riluzole[tiab] OR pexacerfont[tiab] OR Flumazenil[tiab] OR hydroxyzine[tiab] OR doxazosin[tiab] OR uroprost[tiab] OR vigabatrin[tiab] OR galantamine[tiab] OR galanthamine[tiab] OR desipramine[tiab]
	#4	Combine sets	#1 AND (#2 OR #3)
	#5	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table

KQ	Set #	Concept	Strategy
KQ 4 (cannabis use disorder medications)	#1	Population: Cannabis use disorder	(cannabis*[tiab] OR hashish[tiab] OR marihuana[tiab] OR marijuana[tiab]) AND (abuse*[tiab] OR addict*[tiab] OR depend*[tiab] OR discontinu*[tiab] OR disorder*[tiab] OR misuse[tiab] OR use[tiab] OR user*[tiab] OR withdraw*[tiab])
	#2	Intervention: Broad drug therapy terms	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 therapies[ti] OR therapeutic*[ti]))
	#3	Intervention: Named drugs and drug classes	"allosteric modulator*"[tiab] OR acetylcysteine[tiab] OR ambien[tiab] OR amfebutamone[tiab] OR atomoxetine[tiab] OR bupropion[tiab] OR buproprion[tiab] OR buspar[tiab] OR buspirone[tiab] OR (cannabinoid*[tiab] AND (agent*[tiab] OR agonist*[tiab] OR antagonist*[tiab] OR receptor*[tiab])) OR clonidine[tiab] OR clozapine[tiab] OR divalproex[tiab] OR dronabinol[tiab] OR faah*[tiab] OR "fatty acid amidase inhibit*"[tiab] OR "fatty acid amide hydrolase"[tiab] OR escitalopram[tiab] OR fluoxetine[tiab] OR gabapentin[tiab] OR galantamine[tiab] OR guanfacine[tiab] OR guafacine OR horizant[tiab] OR lithium[tiab] OR lofexidine[tiab] OR nabilone[tiab] OR nabiximols[tiab] OR "n acetylcysteine"[tiab] OR nefazodone[tiab] OR neurontin[tiab] OR oxytocin[tiab] OR progesterone[tiab] OR topiramate[tiab] OR "valproate semisodium"[tiab] OR venlafaxine[tiab] OR vilazodone[tiab] OR ziprasidone[tiab] OR zolpidem[tiab] OR Baclofen[tiab] OR Mirtazapine[tiab] OR entacapone[tiab]
	#4	Combine sets	#1 AND (#2 OR #3)
	#5	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table
KQ 5 (cannabis disorder addiction-focused psychotherapies OR psychosocial interventions)	#1	Population: Cannabis use disorder	(cannabis*[tiab] OR hashish[tiab] OR marihuana[tiab] OR marijuana[tiab]) AND (abuse*[tiab] OR addict*[tiab] OR depend*[tiab] OR disorder*[tiab] OR misuse[tiab] OR use[tiab] OR user*[tiab])
	#2	Intervention: Addiction focused psychotherapies OR psychosocial interventions	((behav*[tiab] OR cognitiv*[tiab] OR couple*[tiab] OR famil*[tiab] OR group*[tiab] OR motivation*[tiab] OR psychoso*[tiab]) AND (counsel*[tiab] OR management[tiab] OR therap*[tiab])) OR (cognitiv*[tiab] AND (behav*[tiab] OR therap*[tiab])) OR counsel*[tiab] OR ((community[tiab] OR mutual[tiab]) AND (group*[tiab] OR help[tiab] OR support[tiab])) OR "community reinforcement"[tiab] OR "contingency management"[tiab] OR (famil*[tiab] AND (therap*[tiab] OR train*[tiab])) OR motivational[tiab] OR (motivation*[tiab] AND interview*[tiab]) OR psychoso*[tiab] OR psychoeducat* OR (psychodynamic[tiab] AND therap*[tiab]) OR psychotherap*[tiab] OR "self help"[tiab] OR (support[tiab] AND group*[tiab]) OR (twelve[tiab] AND step[tiab]) OR "12 step"[tiab] OR ((social[tiab] OR interpersonal[tiab]) AND (skill*[tiab] OR train*[tiab]))
	#3	Combine sets	#1 AND #2
	#4	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table

KQ	Set #	Concept	Strategy
KQ 6 (benzodiazepine withdrawal)	#1	Population: benzodiazepine use disorder OR sedative, hypnotic, OR anxiolytic use disorder OR withdrawal	((Hypnotic*[tiab] OR sedative*[tiab] OR alprazolam[tiab] OR Benzodiazepine*[tiab] OR barbiturate*[tiab] OR Barbiturates[tiab] OR Butalbital[tiab] OR chlordiazepoxide[tiab] OR clonazepam[tiab] OR Librium[tiab] OR klonopin[tiab] OR lorazepam[tiab] OR Fiorina[tiab] OR Amytal[tiab] OR Nembutal[tiab] OR Seconal[tiab] OR Phenobarbital[tiab] OR barbs[tiab] OR Ativan[tiab] OR Halcion[tiab] OR Librium[tiab] OR Valium[tiab] OR Xanax[tiab] OR downers[tiab] OR Ambien[tiab] OR zolpidem[tiab] OR Sonata[tiab] OR zaleplon[tiab] OR Lunesta[tiab] OR eszopiclone[tiab] OR diazepam[tiab] OR anoxiolytic[tiab] OR Rohypnol[tiab] OR "chloral hydrate"[tiab] OR glutethimide[tiab] OR methaqualone[tiab] OR Quaalude*[tiab] OR meprobamate[tiab] OR depressant*[tiab] OR flurazepam[tiab] OR dalmane[tiab] OR quazepam[tiab] OR doral[tiab] OR triazolam[tiab] OR estazolam[tiab] OR prosom[tiab] OR temazepam[tiab] OR restoril[tiab] OR trazodone[tiab] OR oleptro[tiab] OR desyrel[tiab] OR amitriptyline[tiab] OR Elavil[tiab] OR doxepin[tiab] OR sinequan[tiab] OR ramelton[tiab] OR rozerem[tiab] OR mirtazapine[tiab] OR remeron[tiab] OR quetiapine[tiab] OR Seroquel[tiab] OR prazosin[tiab] OR minipress[tiab] OR melatonin[tiab] OR "z drug"[tiab] OR "z drugs"[tiab] OR "z-drug"[tiab] OR "z-drugs"[tiab]) AND (abuse[tiab] OR misuse[tiab] OR addict*[tiab] OR disorder*[tiab] OR user[tiab] OR users[tiab] OR withdraw*[tiab] OR detoxif*[tiab] OR taper*[tiab] OR discontinu*[tiab] OR substitute[tiab] OR dependen*[tiab]))
	#2	Intervention: Broad drug therapy terms	Maintenance[ti] OR pharmacotherap*[ti] OR ((drug[ti] OR drugs[ti] OR medication*[ti] OR prescription*[ti]) AND (administrat*[ti] OR compar*[ti] OR treatment*[ti] OR treat[ti] OR treats[ti] treating[ti] OR therapy[ti] OR therapeutic*[ti]))
	#3	Intervention: Named drugs and drug classes	Carbamazepine[tiab] OR ‘valproic acid’[tiab] OR ‘Divalproex sodium’[tiab] OR 'valproate semisodium'[tiab] OR Propranolol[tiab] OR Clonidine[tiab] OR Hydroxyzine[tiab] OR Diphenhydramine[tiab] OR Gabapentin[tiab] OR Promethazine[tiab] OR Metoclopramide[tiab] OR “Calcium carbonate”[tiab] OR Mylanta[tiab] OR “Milk of Magnesia”[tiab] OR Acetaminophen[tiab] OR Ibuprofen[tiab] OR paracetamol[tiab] OR “valporate sodium”[tiab] OR pregabalin[tiab] OR captodiame[tiab] OR captodiamine[tiab] OR paroxetine[tiab] OR antidepressant*[tiab] OR “anti depressant*”[tiab] OR alipdem[tiab] OR busipirone[tiab] OR flumazenil[tiab] OR buspirone[tiab] OR flumazenil[tiab] OR diazepam[tiab]OR clonazepam[tiab] OR Fluoxetine[tiab] OR Prozac[tiab] OR sertraline[tiab] OR ondansetron[tiab] OR “beta block*” OR “beta adrenergic receptor blocking agent”[tiab] OR “beta adrenergic receptor blocking drug*”[tiab] OR “Adrenergic Blocking Drug*”[tiab] OR “Adrenergic Blocking agent*”[tiab]
	#4	Combine sets	#1 AND (#2 OR #3)
	#5	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table

KQ	Set #	Concept	Strategy
KQ 8 (strategies used for promoting active involvement in available mutual help programs)	#1	Population: SUD	((alcohol*[tiab] OR amphetamine*[tiab] OR benzodiazepine*[tiab] OR cannabis[tiab] OR cocaine[tiab] OR drug*[ti] OR ecstasy[tiab] OR heroin[tiab] OR inhalant*[ti] OR marijuana[tiab] OR mdma[tiab] OR methadone[tiab] OR narcotic*[ti] OR opiate*[ti] OR opioid*[ti] OR opium[ti] OR psychostimulant*[tiab] OR solvent*[ti] OR substance*[ti]) AND (abus*[ti] OR abstain*[ti] OR abstinen*[ti] OR addict*[ti] OR behavi*[ti] OR depend*[ti] OR disorder*[ti] OR habit*[ti] OR illegal*[ti] OR illicit*[ti] OR intoxica*[ti] OR misus*[ti] OR use[ti] OR user*[ti] OR usin*[ti] OR utilis*[ti] OR utliz*[ti] OR withdraw*[ti])) OR “substance abuse” OR “drug abuse” OR “opioid abuse” OR “opioid misuse” OR “substance use”
	#2	Intervention: Named facilitation strategies	“twelve step facilitation”[tiab] OR “12 step facilitation”[tiab] OR "TSF"[tiab]OR “Systematic Encouragement and Community Access”[tiab] OR "SECA"[tiab] OR “making AA easier”[tiab] OR “making AA eazier”[tiab] OR “making alcoholics anonymous easier”[tiab] OR “making alcoholics anonymous eazier”[tiab] OR "MAAEZ"[tiab] OR "project match"[tiab] OR "peer alternatives for addiction”[tiab] OR “stimulant abuser groups”[tiab] OR "stage 12"[tiab] OR "network support"[tiab] OR “enhanced referral*”[tiab]
	#3	Intervention: Mutual help programs	“group counseling” OR “group therapy” OR “group support” OR “peer counseling” OR “peer support” OR “peer led” OR “alcoholics anonymous” OR “narcotics anonymous” OR “cocaine anonymous”[tiab] OR "cocaine users anonymous"[tiab] OR "al anon" OR “self help” OR “mutual help” OR “mutual support” OR “community support*” OR "12 step" OR “twelve step” OR "women for sobriety"[tiab] OR "self-management and recovery training"[tiab] OR "smart recovery" OR "lifering" OR "secular organizations for sobriety"[tiab] OR "moderation management" OR meetings[tiab]
	#4	Intervention: General terms for treatment facilitation/referral	buddy OR buddies OR peer[ti] OR peers[ti] OR facilitat*[ti] OR adher*[ti] OR attend*[ti] OR engag*[ti] OR involv*[ti] OR accept*[ti] OR commit*[ti] OR utiliz*[ti] OR utilis*[ti] OR refer[ti] OR referral[ti] OR ((treatment*[tiab] OR therap*[tiab]) AND (adher*[tiab] OR utilis*[tiab] OR utiliz*[tiab] OR refer*[tiab] OR accept*[tiab] OR commit*[tiab] OR engag*[tiab] OR involv*[tiab]))
	#5	Combine sets – specific facilitation strategies	#1 AND #2
	#6	Combine sets –backup search to identify studies on promoting involvement in mutual help programs that do not mention a specific strategy	#1 AND #3 AND #4
	#7	Combine sets	#5 OR #6
	#8	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table

KQ	Set #	Concept	Strategy
KQ 9 (SUD screening)	#1	Population: SUD	((amphetamine*[ti] OR benzodiazepine*[ti] OR cannabis[ti] OR cocaine[ti] OR drug*[ti] OR ecstasy[ti] OR heroin[ti] OR inhalant*[ti] OR marijuana[ti] OR mdma[ti] OR methadone[ti] OR narcotic*[ti] OR opiate*[ti] OR opioid*[ti] OR opium[ti] OR psychostimulant*[ti] OR solvent*[ti] OR substance*[ti]) AND (abus*[ti] OR abstain*[ti] OR abstinen*[ti] OR addict*[ti] OR behavi*[ti] OR depend*[ti] OR disorder*[ti] OR habit*[ti] OR illegal*[ti] OR illicit*[ti] OR intoxica*[ti] OR misus*[ti] OR use[ti] OR user*[ti] OR usin*[ti] OR utilis*[ti] OR utliz*[ti] OR withdraw*[ti])) OR “substance abuse” OR “drug abuse” OR “opioid abuse” OR “opioid misuse” OR “substance use”
	#2	Intervention: Mass screening	screen*[ti] OR question*[ti] OR form[ti] OR forms[ti] OR tool*[ti] OR assessment*[ti] OR scale*[ti] OR instrument*[ti] OR survey*[ti] OR inventory[ti] OR inventories[ti] OR score[ti]
	#3	Intervention: Named screening tools	“cannabis abuse screening test”[tiab] OR “current opioid misuse measure”[tiab] OR “drug abuse screening test”[tiab] OR “emergency medicine providers clinician assessment questionnaire”[tiab] OR “emergency provider impression data collection form”[tiab] OR “opioid risk tool”[tiab] OR “readiness to change questionnaire”[tiab] OR “opioid assessment for patients with pain”[tiab] OR “substance abuse screening inventory”[tiab] OR "4p's"[tiab] OR ((form[tiab] OR forms[tiab] OR tool*[tiab] OR test*[tiab] OR screen*[tiab] OR question*[tiab] OR scale*[tiab] OR survey*[tiab]) AND (assist[tiab] OR cast[tiab] OR crafft[tiab] OR dast*[tiab] OR dhq[tiab] OR dudit[tiab] OR dus[tiab] OR nida[tiab] OR nmassist[tiab] OR rcq[tiab] OR sds[tiab] OR “sip ad”[tiab] OR soapp*[tiab] OR “ssi sa”[tiab] OR “surp-p”[tiab] OR taps[tiab] OR tics[tiab] OR uncope[tiab] OR widus[tiab] OR 'wayne indirect'[tiab]))
	#4	Combine sets	#1 AND (#2 OR #3)
	#5	Apply limits, remove unwanted populations and publication types	See strategies at the end of the table
	#6	Limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table
	#7	Limit to observational study type designs	#5 AND ('between groups'[tiab] OR 'case control'[tiab] OR 'case controlled' OR cohort*[tiab] OR comparison*[tiab] OR comparative[tiab] OR 'control group'[tiab] OR 'controlled study'[tiab] OR 'controlled trial'[tiab] OR 'cross over'[tiab] OR crossover[tiab] OR 'double blind'[tiab] OR 'double blinded'[tiab] OR longitudinal[tiab] OR 'matched controls'[tiab] OR 'observational study'[tiab] OR placebo*[tiab] OR prospective[tiab] OR random*[tiab] OR sham[tiab] OR versus[ti] OR vs[ti])
	#8	Combine sets	#6 OR #7

KQ	Set #	Concept	Strategy
KQ 10 (telehealth and virtual health modalities); KQ 11 (technology-based interventions)	#1	Population: SUD	((alcohol*[tiab] OR amphetamine*[tiab] OR benzodiazepine*[tiab] OR cannabis[tiab] OR cocaine[tiab] OR drug*[ti] OR ecstasy[tiab] OR heroin[tiab] OR inhalant*[ti] OR marijuana[tiab] OR mdma[tiab] OR methadone[tiab] OR narcotic*[ti] OR opiate*[ti] OR opioid*[ti] OR opium[ti] OR psychostimulant*[tiab] OR solvent*[ti] OR substance[ti]) AND (abus*[ti] OR addict*[ti] OR behavi*[ti] OR depend*[ti] OR disorder*[ti] OR habit*[ti] OR illegal*[ti] OR illicit*[ti] OR intoxica*[ti] OR misus*[ti] OR use[ti] OR user*[ti] OR usin*[ti] OR utilis*[ti] OR withdraw*[ti])) OR "substance abuse" OR "drug abuse" OR "opioid abuse" OR "opioid misuse" OR "substance use"
	#2	Intervention: Telehealth (including mental health terms) (KQ 10)	"e health*"[tiab] OR ehealth*[tiab] OR "m health*"[tiab] OR mhealth*[tiab] OR telehealth[tiab] OR telemed*[tiab] OR telepsyc*[tiab] OR telemental*[tiab] OR telebehavior*[tiab] OR teleconsult*[tiab] OR telerehab*[tiab] OR telemonitor*[tiab] OR "tele health"[tiab] OR "tele medicine"[tiab] OR "tele psychiatry"[tiab] OR "tele psychology"[tiab] OR "tele monitor*"[tiab] OR telephone*[tiab] OR phone*[tiab] OR ((online[tiab] OR remote*[tiab] OR video*[tiab] OR virtual[tiab] OR digital[tiab]) AND (monitor*[tiab] OR health*[tiab] OR care[tiab] OR medicine[tiab])) OR videoconferenc*[tiab]
	#3	Intervention: Technology based interventions (KQ 11)	"web based"[tiab] OR website*[tiab] OR cellphone*[tiab] OR "cell phone*"[tiab] OR "cellular phone*"[tiab] OR iphone[tiab] OR ((mobile[tiab] OR wireless[tiab] OR Bluetooth[tiab]) AND (health*[tiab] OR device*[tiab] OR application[tiab] OR app[tiab] OR apps[tiab])) OR "social media"[tiab] OR twitter[tiab] OR tweet[tiab] OR "text messaging"[tiab] OR texting[tiab] OR facebook[tiab] OR instagram*[tiab] OR snapchat*[tiab] OR laptop[tiab] OR (tablet[tiab] AND computer*[tiab]) OR ipad[tiab] OR iwatch[tiab] OR chromebook*[tiab] OR "smartwatch"[tiab] OR "apple watch"[tiab] OR "personal digital assistant"[tiab] OR "technology based"[tiab] OR "app based"[tiab] OR "application based"[tiab] OR "technology supported"[tiab] OR android[tiab] OR helpline*[tiab] OR smartphone*[tiab] OR "smart phone*"[tiab] OR alexa[tiab] OR siri[tiab] OR bixby[tiab] OR digital[ti] OR internet[ti] OR app[ti] OR apps[ti] OR web[ti] OR reset[ti] OR "reset o"[tiab] OR "reset otm"[tiab]
	#4	Combine sets	#1 AND (#2 OR #3)
	#5	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table

KQ	Set #	Concept	Strategy
KQ 12 (addiction-focused mindfulness-based therapies [e.g., ACT, mindfulness-based relapse prevention, Third Wave CBT])	#1	Population: SUD	((alcohol*[tiab] OR amphetamine*[tiab] OR benzodiazepine*[tiab] OR cannabis[tiab] OR cocaine[tiab] OR drug*[ti] OR ecstasy[tiab] OR heroin[tiab] OR inhalant*[ti] OR marijuana[tiab] OR mdma[tiab] OR methadone[tiab] OR narcotic*[ti] OR opiate*[ti] OR opioid*[ti] OR opium[ti] OR psychostimulant*[tiab] OR solvent*[ti] OR substance*[ti]) AND (abus*[ti] OR abstain*[ti] OR abstinen*[ti] OR addict*[ti] OR behavi*[ti] OR depend*[ti] OR disorder*[ti] OR habit*[ti] OR illegal*[ti] OR illicit*[ti] OR intoxica*[ti] OR misus*[ti] OR use[ti] OR user*[ti] OR usin*[ti] OR utilis*[ti] OR utliz*[ti] OR withdraw*[ti])) OR “substance abuse” OR “drug abuse” OR “opioid abuse” OR “opioid misuse” OR “substance use”
	#2	Intervention: Mindfulness based therapies	mindful* OR meditat* OR mbcg[tiab] OR mbsr[tiab] OR micbt[tiab] OR (acceptance[tiab] AND commitment[tiab] AND therapy[tiab]) OR “dialectical behavior”[tiab] OR “dialectical behaviour”[tiab] OR hakomi[tiab] OR morita[tiab] OR “mode deactivation”[tiab] OR “third wave”[tiab] OR yoga OR “deep breathing”[tiab] OR “breathing exercise*”[tiab]
	#3	Combine sets	#1 AND #2
	#4	Apply limits, remove unwanted populations and publication types, limit to RCTs OR SRs OR meta-analyses	See strategies at the end of the table
Limits and hedges applied to each search strategy		Limit to results published 2015-2020	AND ("2015/01/01"[Date - Entry] : "2020/06/30"[Date - Entry])
		Exclude animal and experimental studies	NOT (animal*[ti] OR experimental[ti] OR (vitro[ti] NOT vivo[ti]) OR canine[ti] OR dog[ti] OR dogs[ti] OR mouse[ti] OR mice[ti] OR murine[ti] OR pig[ti] OR pigs[ti] OR piglet*[ti] OR rabbit*[ti] OR rat[ti] OR rats[ti] OR rodent*[ti] OR sheep[ti] OR swine[ti])
		Exclude studies focusing on children	NOT ((adolescen*[ti] OR baby[ti] OR babies[ti] OR boys[ti] OR child*[ti] OR girls[ti] OR infancy[ti] OR infant*[ti] OR juvenile*[ti] OR neonat*[ti] OR newborn*[ti] OR NICU[ti] OR paediatric*[ti] OR pediatric*[ti] OR preschool*[ti] OR school[ti] OR schools[ti] OR teen*[ti] OR toddler*[ti] OR youth*[ti]) NOT (adult*[ti] OR women[ti] OR woman[ti] OR pregnan*[ti]))
		Limit English language	AND (english[Filter]))
		Remove undesired publication and study types (e.g., case reports, conferences, editorials)	NOT (“case report”[ti] OR “a case”[tiab] OR “a patient”[ti] OR “year-old”[tiab] OR comment[ti] OR editorial[ti] OR letter[ti] OR protocol[ti])
		Limit to meta-analyses and SRs	AND (meta-analysis OR meta-analysis[pt] OR meta-analyses OR metaanalysis OR metaanalyses OR "Systematic Review"[pt] OR (systematic*[tiab] AND review*[tiab]) OR “cochrane database syst rev”[journal])
		Limit to RCTs	AND (random*[tw] OR RCT[tw])
		Limit to unprocessed records	(#10 OR #11) AND (inprocess[sb] OR publisher[sb] OR pubmednotmedline[sb])

Appendix I: Participant List

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Appendix J: Abbreviations

Abbreviation	Definition
AA	Alcoholics Anonymous
ACT	acceptance and commitment therapy
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
BCT	behavioral couples therapy
BI	brief intervention
BUP-NX	buprenorphine/naloxone
CBI	combined behavioral intervention
CBT	cognitive behavioral therapy
CBTMET	cognitive behavioral therapy and motivational enhancement therapy
CDC	U.S. Centers for Disease Control and Prevention
CI	confidence interval
CIWA-Ar	Clinical Institute Withdrawal Assessment for Alcohol-Revised
CMS	Centers for Medicare & Medicaid Services
COI	conflict of interest
COR	contracting officer's representative
COWS	Clinical Opiate Withdrawal Scale
CPG	clinical practice guideline
CRA	community reinforcement approach
DEA	U.S. Drug Enforcement Administration
DoD	Department of Defense
DSM	Diagnostic and Statistical Manual of Mental Disorders
EBPWG	Evidence-Based Practice Work Group
ESP	Evidence-Synthesis Program
FDA	U.S. Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HEC	Health Executive Committee
IATP	Individualized Assessment and Treatment Program
iCBT	integrated cognitive behavioral therapy
IDC	individual drug counseling
IOM	Institute of Medicine
IM	intramuscular
ITT	intent-to-treat
KQ	key question
MDD	major depressive disorder
MBRP	mindfulness-based relapse prevention
MET	motivational enhancement therapy

Abbreviation	Definition
MHS	Military Health System
MI	motivational interviewing
MMT	methadone maintenance therapy
MOUD	medication treatment for opioid use disorder
NA	Narcotics Anonymous
NAM	National Academy of Medicine
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NICE	National Institute for Health and Care Excellence
NS	network support
NSDUH	National Survey on Drug Use and Health
OAT	opioid agonist treatment
OTC	over the counter
OTP	opioid treatment program
OUD	opioid use disorder
PGB	pregabalin
PICOTS	the population, intervention, comparison, outcome, timing, and setting
PTSD	posttraumatic stress disorder
RCT	randomized controlled trial
RR	risk ratio
SAMHSA	U.S. Substance Abuse and Mental Health Service Administration
SASQ	Single Item Alcohol Screening Questionnaire
SC-BPN	buprenorphine subcutaneous depot
SR	systematic review
SSRI	selective serotonin uptake inhibitors
SUD	substance use disorder(s)
TCA	tricyclic antidepressants
TM	text messaging
TSF	12-step facilitation
U.S.	United States
UCMJ	Uniform Code of Military Justice
UDT	urine drug testing
USPSTF	U.S. Preventive Services Task Force
VA	Department of Veterans Affairs
VHA	Veterans Health Administration
XR	extended-release
12SNA	12-step Narcotics Anonymous

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