VA/DoD Clinical Practice Guidelines

VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders

Provider Summary

Version 4.0 | 2021

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

Department of Veterans Affairs

Department of Defense

Provider Summary

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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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

The full VA/DoD SUD CPG, as well as additional toolkit materials including a pocket card and patient summary, can be found at: https://www.healthquality.va.gov/guidelines/MH/sud/.

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

Recommendations

The following evidence-based clinical practice recommendations were made using a systematic approach considering four domains as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (see Appendix A in the full VA/DoD SUD CPG). 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).

Table 1. Recommendations

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	***α. 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

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Treatment (cont.)	*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
	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

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Treatment (cont.)	*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
	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

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
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
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 in the full VA/DoD SUD CPG.

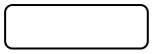
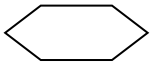
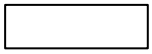
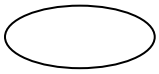
[b] For additional information, see Recommendation Categorization and Appendix D in the full VA/DoD SUD CPG.

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:

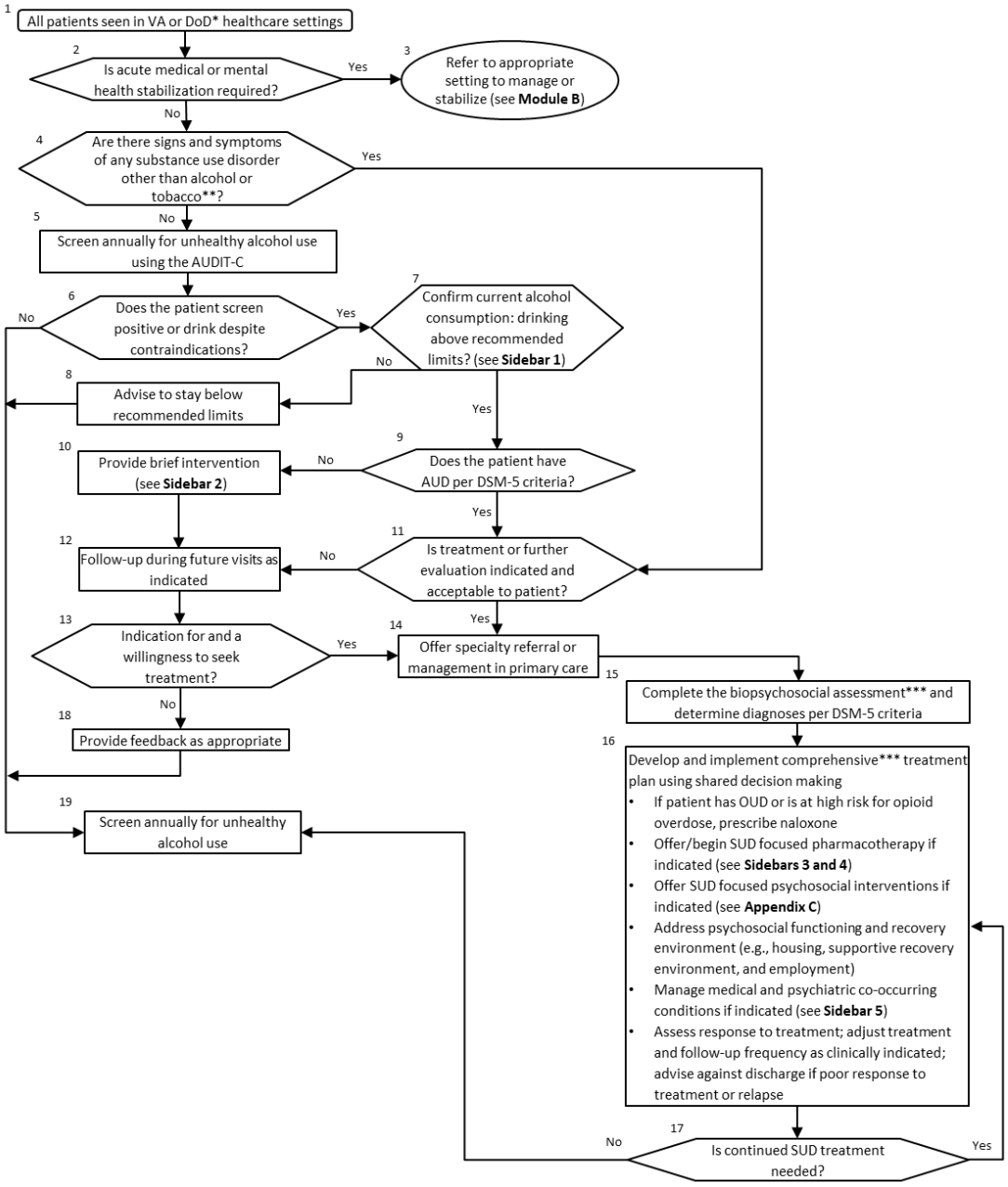
- An ordered sequence of steps of care
- Decisions to be considered
- Recommended decision criteria
- Actions to be taken

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.(2) 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

For alternative text descriptions of the algorithm, please refer to Appendix G in the full VA/DoD SUD CPG.

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 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).

*** 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

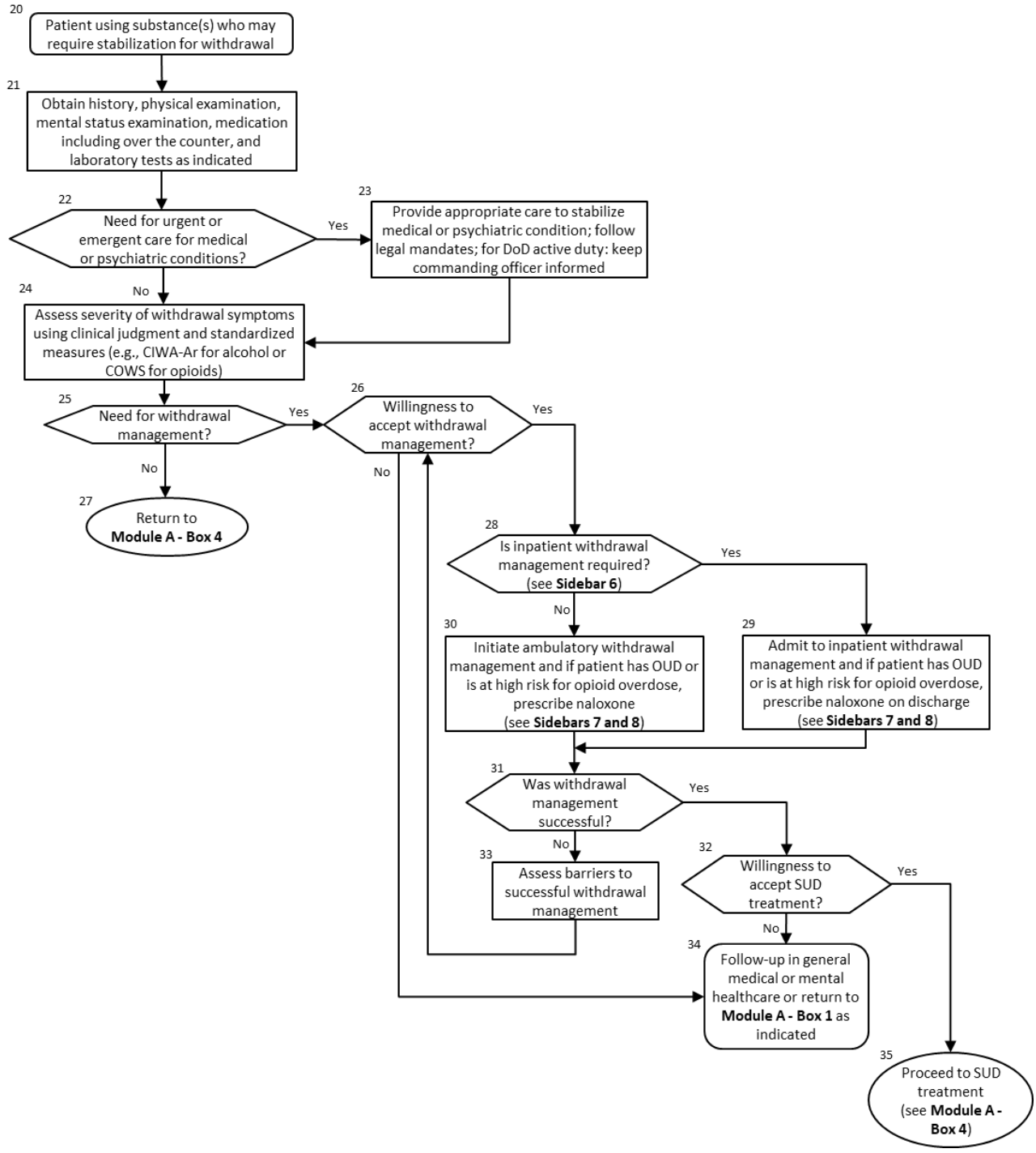
Sidebar 4: Components of Addiction-focused Medical Management
• Monitoring adherence, response to treatment, and adverse effects • Education about AUD/OUD, health consequences, and treatments • Encouragement to abstain from illicit opioids and other addictive substances • Encouragement to attend and 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

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

Scope of the CPG

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 in the full VA/DoD SUD CPG for additional information on the evidence review methodology). This CPG is not intended to serve as a standard of care.

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.

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 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).

Highlighted Features of this Guideline

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 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 in the full VA/DoD SUD CPG.

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. The CPG also includes research priorities that identify areas needing additional research (see the Research Priorities section in the full VA/DoD SUD CPG).

Methods

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.(3) The *Guideline for Guidelines* is available at http://www.healthquality.va.gov/policy/index.asp. This CPG also aligns with the National Academy of Medicine's (NAM) principles of trustworthy CPGs (e.g., explanation of evidence quality and strength, the management of conflicts of interest [COI], interdisciplinary stakeholder involvement, use of systematic review, and external review).(4) Appendix A in the full VA/DoD SUD CPG provides a detailed description of the CPG development methodology.

The Work Group used the Grading of Recommendations Assessment, Development and Evaluation (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: 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) (see Grading Recommendations in the full VA/DoD SUD CPG).(5)

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.(6) 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).

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.

The GRADE of each recommendation made in the 2021 CPG can be found in the section on Recommendations. Additional information regarding the use of the GRADE system can be found in Appendix A in the full VA/DoD SUD CPG.

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).(7, 8) The categories and definitions can be found in Table 3.

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) (7) and Garcia et al. (2014) (8)

[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.

Abbreviation: CPG: clinical practice guideline

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*Additional contributor contact information is available in Appendix I in the full VA/DoD SUD CPG.

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.(9, 10) 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.

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.(11) 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.

Pharmacotherapy Considerations

Table 4. 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

Topic Area	Naltrexone Oral	Naltrexone Injectable	Acamprosate	Disulfiram	Topiramate	Gabapentin
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)	
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

Topic Area	Naltrexone Oral	Naltrexone Injectable	Acamprosate	Disulfiram	Topiramate	Gabapentin
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.(12) 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.(12) 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.(12, 13)

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.(14) 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.(15)

Table 5. Pharmacotherapy for Opioid Use Disorder[a]

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

[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.

Topic Area	Methadone	Buprenorphine/Naloxone or Buprenorphine	Buprenorphine Depot Injectable	Naltrexone Injectable
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
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	• 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)	• 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	• 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
Warnings/Precautions (cont.)	• Neonatal withdrawal has been reported following use of buprenorphine by pregnant women • Multiple drug interactions. See Drug Interactions below for more details.	• 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	• 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	
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

Topic Area	Methadone	Buprenorphine/Naloxone or Buprenorphine	Buprenorphine Depot Injectable	Naltrexone Injectable
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)
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

Topic Area	Methadone	Buprenorphine/Naloxone or Buprenorphine	Buprenorphine Depot Injectable	Naltrexone Injectable
Patient Education	• Strongly advise patient against self-medicating with CNS depressants during methadone therapy • Serious overdose and death may occur if benzodiazepines, sedatives, tranquilizers, antidepressants, or alcohol are taken with methadone • Store in a secure place out of the reach of children • Strongly advise patient to continue in long-term methadone maintenance • If discontinuing methadone, recommend transition to extended-release injectable naltrexone • Serious overdose and death may occur if patient relapses to opioid use after withdrawal from methadone	• Strongly advise patient against self-medicating with CNS depressants during buprenorphine therapy • Serious overdose and death may occur if benzodiazepines, sedatives, tranquilizers, antidepressants, or alcohol are taken with buprenorphine • Store in a secure place out of the reach of children • Strongly advise patient to continue in long-term buprenorphine maintenance • If discontinuing buprenorphine, recommend transition to extended-release injectable naltrexone • Serious overdose and death may occur if patient relapses to opioid use after withdrawal from buprenorphine • 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 6. 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

Psychosocial Intervention Considerations

Table 7. 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.(16, 17)

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.(18-21)

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.(22, 23)

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.(24)

E. Individual Drug Counseling

The approach to IDC is manualized (25) 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.(26)

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).(27) Network support based on TSF engages patients in pro-recovery organizations other than AA and has proved to be efficacious in randomized trials.(28, 29)

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Access to the full guideline and additional resources are available at the following link:
https://www.healthquality.va.gov/guidelines/MH/sud/