COURSE #95300 — 8 CONTACT HOURS/CREDITS RELEASE DATE: 05/01/23 EXPIRATION DATE: 04/30/26

Substance Use Disorders and Pain Management: MATE Act Training

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for all healthcare professionals who may alter prescribing practices or intervene to help meet the needs of patients with substance use disorders.

Accreditations & Approvals

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This activity has been designated for 8 Lifelong Learning (Part II) credits for the American Board of Pathology Continuing Certification Program.

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NetCE designates this continuing education activity for 8 ANCC contact hours.

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NetCE designates this continuing education activity for 8 pharmacotherapeutic/pharmacology contact hours.

AACN Synergy CERP Category A.

NetCE designates this activity for 8 hours ACPE credit(s). ACPE Universal Activity Numbers: JA4008164-0000-23-010-H08-P and JA4008164-0000-23-010-H08-T.

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This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency, and California Assembly Bill 241, Implicit Bias.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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Course Objective

The purpose of this course is to provide clinicians who prescribe or distribute controlled substances with an appreciation for the complexities of managing patients with substance use disorders and comorbid pain in order to provide the best possible patient care and to prevent a growing social problem.

Learning Objectives

Upon completion of this course, you should be able to:

1. Outline substance use disorder risk factors, screening, and diagnosis.
2. Describe the role of psychosocial therapies in the management of substance use disorders.
3. Compare and contrast available pharmacotherapeutic options for the treatment of alcohol, tobacco, and opioid use disorders.
4. Discuss the impact of polysubstance use and co-occurring mental disorders and substance use disorder presentation and treatment.
5. Review legal and ethical issues related to substance use disorder treatment.
6. Create comprehensive treatment plans for patients with pain that address patient needs as well as drug diversion prevention.
7. Evaluate behaviors that may indicate drug seeking or diverting as well as approaches for patients suspected of misusing opioids.
8. Identify state and federal laws governing the proper prescription and monitoring of controlled substances.

Pharmacy Technician Learning Objectives

Upon completion of this course, you should be able to:

1. Outline key components of the assessment and treatment of substance use disorders.
2. Evaluate treatment plans for the safe and effective management of pain, including in those with existing substance use disorders.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Substance use disorders continue to be an important health issue in the United States. The fifth edition (text revision) of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5-TR) includes criteria for substance use disorder involving alcohol; cannabis; hallucinogens; inhalants; opioids; sedatives, hypnotics, or anxiolytics; stimulants; tobacco (nicotine); and other (or unknown) substances [1]. Excluding tobacco use disorder, the most common substance use disorders in the United States are [2]:

- Alcohol use disorder (29.5 million)
- Cannabis use disorder (16.3 million)
- Prescription opioid use disorder (5.0 million)
- Methamphetamine use disorder (1.6 million)

Substance use disorders can lead to significant problems in all aspects of a person's life, and appropriate assessment and management of substance use is a priority in patient care.

The presence of substance use disorders can complicate the treatment or management of comorbid medical conditions. Given the ongoing prescription opioid (and illicitly manufactured fentanyl) use and overdose epidemic in the United States and the widespread incidence of chronic pain, opioid prescribing and optimum safe pain management is a public health concern. All clinicians should have good knowledge of the available options for substance use disorder treatment and for safe opioid prescribing and dispensing.

Coordinated care is critical to achieve positive outcomes. Coordinating treatment for comorbidities, including mental health conditions, is an important part of treating substance use disorders and pain alike.

SUBSTANCE USE DISORDER SCREENING AND DIAGNOSIS

According to the 2021 National Survey on Drug Use and Health, 46.3 million Americans 12 years of age or older had a substance use disorder in the past year [2]. Substance use disorders are treatable, chronic diseases characterized by a problematic pattern of use of a substance or substances leading to impairments in health, social function, and control over substance use. It is a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite harmful consequences. These disorders range in severity and can affect people of any race, gender, income level, or social class.

RISK FACTORS

Researchers who study risk factors have developed models of how known risk factors may interact to create pathways that lead to substance use disorders. Of course, not all persons who use drugs regarded as having a high liability of misuse end up becoming addicted to the drug.

Genetic Predisposition

Research has shown that genetic factors play a strong role in whether a person develops a substance use disorder, accounting for 40% to 60% of the risk [3; 4; 5]. In fact, family transmission of substance use disorder, particularly alcohol use disorder, has been well established. Individuals who have relatives with substance use disorder are at three- to five-times greater risk of developing substance use disorder than the general population. The presence of substance use disorder in one or both biologic parents is more important than the presence of substance use disorder in one or both adoptive parents. The genetic risk increases with the number of relatives with substance use disorder and the closeness of the genetic relationship [5]. However, most children of parents with substance use disorder do not develop disorders, and some children from families where substance use is not a problem develop disorders when they get older.

Children with Conduct Problems

One model focuses on children who have temperaments that make it difficult for them to regulate their emotions and control their impulses. Clearly, these children are difficult to parent, and if one or both of their parents have a substance use disorder, it is likely that they will be poorly socialized and have trouble getting along in school [6; 7]. Poor academic performance and rejection by more mainstream peers at school may make it more likely for these children to join peer groups where drinking and other risky behaviors are encouraged. Parents with substance use disorders will likely not monitor their children closely and will lose control over them at an early age. These children will begin using substances early, often before 15 years of age [8]. If such a child is genetically predisposed to substance use disorders, these environmental factors may further increase the tendency [9].

Stress and Distress

Another model of risk factors leading to substance use disorder focuses on substance use to regulate inner distress [10]. Some children have temperaments that make them highly reactive to stress and disruption. Regardless of the child's family environment, he or she maintains higher levels of inner distress (anxious and depressed feelings) than other children. When they first drink or use a substance, the inner distress dissipates for a while. This leads to more substance use and may lead to substance use disorder. More research is required before the role of stress as a risk factor in alcohol use disorders is understood.

Adverse childhood experiences, particularly sexual abuse, family rejection, and parental neglect, are independent risk factors for substance use disorders [11]. Adverse childhood experiences are linked with depression in adulthood, which itself is a risk factor for substance use disorder. This correlation can be modulated by resilience, which can also be a result of adverse childhood experiences.

Other Mental Disorders

Mental disorders can contribute to substance use and substance use disorders. Certain psychiatric disorders, including anxiety, depression, or post-traumatic stress disorder, have been linked to substance misuse, likely a form of self-medication. Additionally, brain changes in people with mental disorders may enhance the rewarding effects of substances, making it more likely they will continue to use the substance [12].

Environmental Stimuli

The expected drug effect and the setting of use (context of administration) play important roles in the social learning of drug use. Opioids and other drugs that increase dopamine turnover lead to conditional responses, and use may become conditioned to the activities of daily living. As a result, environmental stimuli can become powerfully associated with substance use, which can trigger cravings for the drug [13]. The visibility of pharmaceutical marketing and advertising of medications may also play a role by changing the attitudes toward ingestion of these agents [13]. For youth, a social learning aspect to drug use is likely, based on the modeling of drug use by adults in their families and social networks [13].

SCREENING

A variety of screening and assessment tools are available, with applicability for various substances, patient populations, and screening environments (***Table 1***).

The Tobacco, Alcohol, Prescription medication, and other Substance Use (TAPS) Tool is validated for use with adults to generate a risk level for each substance class. It can be self-administered or conducted via clinician interview and combines screening and brief assessment of past 90-day problematic use into one tool [14]. The TAPS Tool has two components. The first component (TAPS-1) is a four-item screen for tobacco, alcohol, illicit drugs, and non-medical use of prescription drugs. If an individual screens positive on TAPS-1 (i.e., reports other than "never"), the tool will automatically begin the second component (TAPS-2), which consists of brief substance-specific assessment questions to arrive at a risk level for that substance. Clinicians are encouraged to provide positive feedback to patients who screen negative and support their choice to abstain from substances. The tool can be accessed online at https://nida.nih.gov/taps2/#/.

DIAGNOSIS

As noted, the DSM-5-TR defines substance use disorder as a problematic pattern of substance use, leading to clinically significant impairment or distress. While criteria are outlined for specific substances in the DSM-5-TR, the components are generally the same regardless of substance used. The diagnosis of substance use disorder is made by meeting two or more criteria in a one-year period [1]:

- Substance taken in larger amounts or over a longer period than was intended
- A persistent desire or unsuccessful efforts to cut down or control use
- Excessive time spent to obtain, use, or recover from using the substance
- Craving, an intense urge to use
- Substance use interferes with obligations
- Continued use despite life disruption
- Reduction or elimination of important activities due to use
- Recurrent use in physically hazardous situations
- Continued use despite physical or psychologic problems
- Tolerance
  - Need for increased doses of the substance for the desired effect
  - A markedly diminished effect with continued use of the same amount
- Withdrawal

In the case of opioid use disorder, the criteria for tolerance and withdrawal are not considered to be met for those taking opioids solely under appropriate medical supervision.

SCREENING AND ASSESSMENT TOOLS CHART						
Tool	**Substance Type**		**Patient Age**		**Administration Method**	
	Alcohol	**Drugs**	**Adults**	**Adolescents**	**Self-Administered**	**Clinician-Administered**
Screening Tools						
Screening to Brief Intervention (S2BI)	X	X		X	X	X
Brief Screener for Alcohol, Tobacco, and other Drugs (BSTAD)	X	X		X	X	X
Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS)	X	X	X		X	X
Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide (NIAAA)	X			X		X
Opioid Risk Tool – OUD (ORT-OUD) Chart		X	X		X	
Assessment Tools						
Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS)	X	X	X		X	X
CRAFFT	X	X		X	X	X
Drug Abuse Screen Test (DAST-10)[a]		X	X		X	X
Drug Abuse Screen Test (DAST-20: Adolescent version)[a]		X		X	X	X
Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide (NIAAA)	X			X		X
[a]Tools with associated fees						
Source: [14]						*Table 1*

SUBSTANCE USE DISORDER TREATMENT

All substance use disorder treatment plans should reflect the patient's most important goals and establish measurable and achievable steps toward achieving those goals. As such, all treatment plans will be individualized and created in collaboration with the patient. This recovery roadmap also requires that clinicians communicate with clear, nonstigmatizing language regarding the patient's condition and options.

TREATMENT PLANNING

Assessing Readiness to Change

Readiness to Change is Dimension 4 of the American Society of Addiction Medicine's (ASAM's) Six Dimensions of Multidimensional Assessment (also known as the ASAM Criteria) that is the standard for placement, continued stay, transfer, or discharge of patients with substance use disorder and co-occurring conditions [15]. Several factors influence a person's readiness and ability to change behaviors. It is useful to help patients to weigh the risks of continued substance use and benefits of decreasing or eliminating substance use. Healthcare professionals can help motivate the patient to become ready for treatment if the patient appears ready to change.

Is the patient ready to change? The role of motivation is an important part of changing behavior.

Motivational Interviewing

Motivational interviewing is a method of counseling designed to enhance patients' motivation to change by helping them explore and resolve their ambivalence about making the change [16]. It is a collaborative, non-confrontational, "guiding" approach. In substance use disorder, motivational interviewing utilizes active listening to understand how the patient feels about his or her substance use in an effort to uncover any ambivalence [17]. The healthcare provider elicits the patient's own views regarding consequences of continuing to use and benefits of quitting and asks permission to share additional information on risks when necessary. Goals are developed collaboratively, based on the patient's current readiness to change. Originally developed as an intervention for alcohol use disorder, it has shown promise as a successful strategy for other substances as well.

PSYCHOSOCIAL THERAPY

Treatment of substance use and dependence with psychosocial or behavioral therapy is based on the assumption that addictive behavior is developed and maintained by specific mechanisms [18]:

- Expectancies and modeling
- Reinforcing properties of the drug
- Secondary social reinforcement

The goal of these types of treatments is to modify drug-seeking and other behavioral aspects of drug dependency [19]. Psychosocial therapy and pharmacotherapy are not mutually exclusive; in fact, some drug therapies for substance abuse are considered useless without a psychosocial/behavioral component [18; 19].

Psychosocial therapies for substance use disorders can be divided into two broad categories. The first category consists of therapies that were originally developed for patients with anxiety and depression and modified for use with patients with substance use disorders. This group of therapeutic approaches includes cognitive-behavioral therapy (CBT), the behavioral therapies, and interpersonal therapy.

The second group of psychosocial therapies was developed explicitly for patients with substance use disorders and includes motivational interviewing and motivation enhancement therapy [19; 20]. All psychotherapies are intended to be delivered in a supportive, empathic manner that minimizes confrontation.

For patients with alcohol use disorder, the Department of Veterans Affairs Work Group recommends 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

(https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPG.pdf. Last accessed April 27, 2023.)

Strength of Recommendation: Strong for

Drug counseling is a widely used therapy approach with patients with substance use disorders. It consists of a focus on abstinence, problem solving, and 12-step orientation and involvement. Drug counseling is usually provided by counselors who have a certificate in addiction counseling. A fair number of addiction counselors are themselves recovering from alcohol and/or substance use disorders [20].

Contingency Management

There is considerable evidence that substance use is sensitive to the application of contingencies. Contingencies occur on a spectrum from contrived to naturalistic. Contingency management and vouchers are examples of contrived interventions, while 12-step programs are examples of naturalistic interventions [21]. Contrived contingencies may be effective in initially engaging patients in abstinence, but relapse to drug use may occur following removal of the reinforcer. In contrast, naturalistic contingencies are more likely to maintain the initial gains made by the patient and to facilitate the sustained change of behavior over time [22].

The goal of contingency management interventions is to increase the opportunity cost of substance use by arranging an environment where drug use results in the forfeiture of a predetermined item or privilege, referred to as an alternate reinforcer [23]. Treatment with a contingency management component was first used with cocaine-abusing methadone patients, a highly suitable population for two reasons: cocaine abuse is prevalent among patients with opioid use disorder receiving methadone maintenance, and methadone patients are required to report to the clinic daily to receive their medication under staff supervision. Daily clinic appointments are often considered a significant constraint on employment, travel, and other activities. Patients who are able to abstain from drugs of abuse, as measured by a urine drug screen, may be allowed several days of take-home methadone doses, which can act as a behavioral contingent [24]. Several studies have shown that this contingent condition has led to greater treatment retention and reductions in cocaine use than those found in comparison treatment conditions, although this effect dissipates with longer-term follow-up [22; 25; 26; 27].

Community Reinforcement

Community reinforcement approaches are biopsychosocial interventions designed to engage and change the lifestyle of the drug abuser by addressing the role of environmental cues and alternative reinforcers in influencing behavior. The theoretical basis of the community reinforcement approach is that substance abuse is maintained by substance-related reinforcers as well as by the absence of competing alternative reinforcers. The primary goal of the community reinforcement approach is to build and strengthen relationships, recognize appropriate leisure activities, and identify vocational interests of the patient to provide competing reinforcement with substance use and the drug-using lifestyle [28].

The community reinforcement approach aims to increase abstinence by increasing or highlighting the opportunity cost of relationships and social support the patient stands to lose through drug use [22]. In addition to integrating cognitive-behavioral and, in some cases, pharmacologic approaches, community reinforcement approaches may also include the use of vouchers, whereby tokens are given to the patient for producing substance-free urine samples, which are then used to purchase goods and services desired by the patient.

A review of four studies utilizing a community reinforcement approach with patients with substance use disorder found evidence that a community reinforcement approach employing abstinence-contingent incentives in the form of vouchers was more effective in promoting abstinence than community reinforcement approaches using noncontingent incentives and usual care. Patients assigned to community reinforcement incorporating abstinence-contingent incentives experienced a greater reduction in disease severity as measured by the Addiction Severity Index than comparison groups [28]. Despite early, promising reports of community reinforcement with patients with alcohol use disorder and evidence that patients receiving community reinforcement approaches have demonstrated more favorable drug use outcomes than patients receiving standard outpatient counseling, a community reinforcement approach is seldom used because of the relatively high cost and labor intensity [19; 29].

Motivational Interventions

Motivational interventions for substance use disorders stem from the theory that targeting and enhancing motivation to quit drugs will increase positive outcome; positive outcome is increased when motivation comes internally rather than when it is externally imposed. Specifically, motivational enhancement therapy is based on the Transtheoretical Stages of Change Theory, which postulates that patients pass through a series of stages of thought, planning, and action in the process of behavior change [30].

Motivational enhancement therapy is intended to enhance motivation and commitment to change, activate patient resources, and facilitate movement along the readiness-to-change spectrum [31]. Motivational enhancement therapy helps patients build internal motivation through the resolution of issues related to ambivalence. The therapeutic approach is characterized by nonconfrontive, nonjudgmental interviewing that helps the patient consider the pros and cons of change. Motivational enhancement therapy also strives to enhance patient self-efficacy [30]. Motivational enhancement therapy seems to be more effective in patients with low initial levels of motivation when used for patients with substance use disorder. It tends to result in less relapse to use and fewer total days of use [32].

Coping and Social Skill Training

Coping and social skill training (CSST) evolved from social learning theory and is used to improve the inadequate coping skills found in many persons with substance use disorders, including deficits in regulation of emotion and in effectively coping with social situations. CSST addresses four primary areas [33]:

- Interpersonal skills
- Cognitive and affective regulation
- Coping skills to manage stressful life events
- Coping skills when substances or substance-related cues are encountered

An added emphasis on drug-related cues is used when CSST is employed with patients with certain substance use disorders (e.g., cocaine, opioids) [33].

CSST has incorporated these findings into the treatment approach used with patients with substance use disorders. Preliminary results indicate some benefit of substance-specific CSST in reducing frequency of substance use and increasing duration of abstinence, although these results have not been replicated in subsequent research [32; 33].

Drug Counseling

CBT is among the most frequently evaluated approaches used to treat substance use disorders [34; 35]. CBTs have been shown to be effective in several clinical trials of substance users [36]. Characteristics of CBTs include:

- Social learning and behavioral theories of drug abuse
- An approach summarized as "recognize, avoid, and cope"
- Organization built around a functional analysis of substance use (i.e., understanding substance use with respect to its antecedents and consequences)

Skill training focused on strategies for coping with craving, fostering motivation to change, managing thoughts about drugs, developing problem-solving skills, planning for and managing high-risk situations, and cultivating drug refusal skills

Basic principles of CBTs are that [37; 38]:

- Basic skills should be mastered before more complex ones are given.
- Material presented by the therapist should be matched to patient needs.
- Repetition fosters the development of skills.
- Practice is needed for mastery of skills.
- The patient is an active participant in treatment.
- Skills taught are general enough to be applied to a variety of problem areas.

Structured behavior therapy techniques can be effective components of substance use disorder treatment. Contingent incentive procedures are designed to enhance a patient's motivation to meet treatment goals by offering concrete rewards for specific performance outcomes.

Behavioral therapy techniques are often part of CBT. In this approach, substance use is believed to develop from changes in behavior and a reduction in opportunities for reinforcement of positive experience. The goal is to increase the person's engagement in positive or socially reinforcing activities. Techniques such as having patients complete a schedule of weekly activities, engaging in homework to learn new skills, role-playing, and behavior modification are used. Activity, exercise, and scheduling are major components of this approach based on the following:

- Patients with substance use disorders require motivation and skills to succeed in stopping drug use.
- Research has shown that drug abuse behavior can be reduced by offering contingent incentives for abstinence.
- The most striking successes have come from positive reinforcement programs that provide contingent incentives for abstinence using money-based vouchers as rewards.
- Research provides examples, but treatment providers may need to be creative in discovering reinforcers that can be used for contingency management in their own clinical settings.

Family therapy is a highly effective treatment for alcohol use disorder, especially in adolescents. While most treatments emphasize the individual as the target of intervention, the defining characteristic of family therapy is the transformation of family interactions. Repetitive patterns of family interactions are the focus of treatment. Changing these patterns results in diminished antisocial behavior including alcohol abuse. Family therapy can work with a broad range of family and social network populations. Family therapy approaches have developed specific interventions for engaging and keeping reluctant, unmotivated adolescents and family members in treatment.

PHARMACOTHERAPY FOR DETOXIFICATION AND ABSTINENCE

A variety of medications have been approved to assist in cessation of the use of opioids, alcohol, and nicotine (***Table 2***). Any time pharmacotherapy is initiated, is important that a collaborative, patient-centered approach is undertaken, with all members of the care team working together to best meet the needs of the specific patient. Unique, individual physiology and metabolism can impact medication pharmacodynamics; this should be considered in each treatment plan.

Alcohol Use Disorder

Several medications are available to help treat alcohol use disorder [40; 41]. Some are used for detoxification and others are used to prevent relapse. Research has shown that medications are most effective when used in conjunction with other therapies.

Disulfiram

Disulfiram, commonly known as Antabuse, was the first drug to be made available for the treatment of alcohol use disorder. It was approved for treatment of alcohol use disorder by the U.S. Food and Drug Administration (FDA) in 1951 and has been used safely and effectively for decades. It works by blocking an enzyme, aldehyde dehydrogenase, that helps metabolize alcohol. Taking even one drink while on disulfiram causes the alcohol at the acetaldehyde stage to accumulate in the blood. This produces nausea, vomiting, sweating, and even difficulty breathing. More alcohol in the patient's system produces more severe reactions (e.g., respiratory depression, cardiovascular collapse, unconsciousness, convulsions, death) [41; 42]. Patients must also be mindful of consuming even minute amounts of alcohol in foods, over-the-counter medications, mouthwash, and even topical lotions. Disulfiram can be effective for people who have completed alcohol withdrawal, are committed to staying sober, and are willing to take the medication under the supervision of a family member or treatment program [41]. Due to more modern and improved medication modalities, many clinicians prescribe disulfiram as a last-resort intervention. Although widely used, it is less clearly supported by clinical trial evidence [43; 44; 45].

MEDICATIONS USED IN THE TREATMENT OF SUBSTANCE USE DISORDERS					
Drug	**Dose Range**	**Typical Starting Dose**	**Potential Adverse Effects**	**Route(s)**	**DEA Schedule**
Opioid Use Disorder					
Buprenorphine/ naloxone (Bunavail, Suboxone, Zubsolv)	Buprenorphine: 0.7–24 mg/day Naloxone: 0.18–6 mg/day	4/1 mg/day	Pain, headache, nausea, diaphoresis	Buccal film, sublingual film, sublingual tablet	CIII
Methadone (Dolophine, Methadose, DISKETS)	20–120 mg/day	20–30 mg/day	Pruritus, constipation, cardiac abnormalities	PO, IV	CII
Naltrexone (Vivitrol)	PO: 25-50 mg/day IM: 380 mg/week	PO: 25 mg/day IM: 380 mg/month	Injection site reactions, anxiety, syncope	PO, IM	Not scheduled
Buprenorphine (Belbuca, Buprenex, Butrans, Probuphine, Sublocade)	SQ: 100–300 mg/ month SL: 2–24 mg/day	SQ: 300 mg/month Implant: 4 implants SL: 2–4 mg/day	Few	Sublingual tablet, subdermal implant, SQ injection	CIII
Alcohol Use Disorder					
Acamprosate (Campral)	666 mg TID	666 mg TID	Diarrhea	PO	Not scheduled
Naltrexone (Vivitrol)	PO: 25–100 mg/day IM: 380 mg/month	PO: 50 mg/day IM: 380 mg/month	Injection site reactions, anxiety, syncope	PO, IM	Not scheduled
Disulfiram	125–500 mg/day	250 mg/day	Bitter taste, impotence, drowsiness	PO	Not scheduled
Tobacco Use Disorder					
Bupropion, sustained-release (Zyban)	150 mg daily or BID	150 mg/day	Weight loss, constipation, agitation, xerostomia, nausea	PO	Not scheduled
Nicotine	Gum: Up to a maximum 30 pieces/day Inhaler: 6–16 cartridges/day Lozenge: Titrate to 1 lozenge every 4 to 8 hours Nasal spray: Maximum 80 sprays/day Patch: One patch/day for 8 weeks	Gum: 1 to 2 pieces/ hour (2 mg/piece) Inhaler: 6 cartridges/ day Lozenge: One lozenge every 1 to 2 hours Nasal spray: 1 spray in each nostril once or twice per hour Patch: One patch/day	Oral irritation, headache, dyspepsia, nasal discomfort, cough, rhinitis	PO, intranasal, transdermal	Not scheduled
Varenicline (Chantix)	1 mg BID up to 12 weeks	0.5 mg/day	Nausea, abnormal dreams, headache	PO	Not scheduled

BID = two times per day, DEA = Drug Enforcement Administration, IM = intramuscular, IV = intravenous, PO = oral, SL = sublingual, SQ = subcutaneous, TID = three times per day.

Source: [39] *Table 2*

The recommended dose for disulfiram is 250 mg/day, which can be increased to 500 mg based upon whether a patient experiences the disulfiram-ethanol reaction [46]. Doses may need to be reduced in patients older than 60 years of age [41]. Labeling for disulfiram includes several precautions regarding drug-drug interactions; therefore, caution should be used when prescribing it to older adults at risk for polypharmacy [41]. Due to the physiologic changes that occur with use, use of disulfiram is not recommended in patients with diabetes, cardiovascular or cerebrovascular disease, or kidney or liver failure. It also is contraindicated in the presence of psychoses and pregnancy and in those with high levels of impulsivity and suicidality [41].

Naltrexone

Naltrexone (ReVia) is an opioid antagonist that interferes with the rewarding or pleasurable effects of alcohol and reduces alcohol craving [47; 48; 49]. The exact mechanisms by which naltrexone induces the reduction in alcohol consumption observed in patients with alcohol use disorder is not entirely understood, but preclinical data suggest involvement of the endogenous opioid system [41]. Naltrexone has been shown to reduce alcohol relapses, decrease the likelihood that a slip becomes a relapse, and decrease the total amount of drinking [41]. The FDA approved the use of oral naltrexone in alcohol use disorder in December 1994 [41; 49]. In 2006, the FDA approved an extended-release injectable formulation, which is indicated for use only in patients who can refrain from drinking for several days prior to beginning treatment [41]. In 2010, the FDA approved the injectable naltrexone for the prevention of relapse to opioid dependence following opioid detoxification [41].

After a complete history, physical exam, and laboratory testing, most patients are started on 50 mg orally per day [39]. For most patients, this is the safe and effective dose of naltrexone. However, in a four-month study period, the COMBINE study demonstrated efficacy of naltrexone at a dose of 100 mg daily [50]. Some treatment providers give patients a naltrexone identification card or ask them to order a MedicAlert bracelet that clearly indicates that they are maintained on an opioid antagonist, so if they need an opiate drug or medication for pain relief, the dose of the pain medication can be adjusted higher. Meta-analyses have revealed that approximately 70% of previous clinical trials that measured reductions in "heavy or excessive drinking" demonstrated an advantage for prescribing naltrexone over placebo [51]. In another trial, naltrexone was determined to have the greatest impact on reducing daily drinking when craving for alcohol was highest [52]. The approved dose of the extended-release formulation is 380 mg IM once per month. Pretreatment with oral naltrexone is not required before induction onto extended-release injectable naltrexone [41].

The most common side effects of naltrexone are light-headedness, diarrhea, dizziness, and nausea. Pain or tenderness at the injection site is a side effect unique to the extended-release injectable formulation [41]. Most side effects tend to disappear quickly in most patients. Naltrexone is not recommended for patients with acute hepatitis or liver failure, for adolescents, or for pregnant or breastfeeding women [41; 50]. Weight loss and increased interest in sex have been reported by some patients. In general, patients maintained on opioid antagonists should be treated with nonopioid cough, antidiarrheal, headache, and pain medications. The patient's family or physician should call the treating physician if questions arise about opioid blockade or analgesia. It is important to realize that naltrexone is not disulfiram; drinking while maintained on naltrexone does not produce side effects or symptoms.

Naltrexone works best when it is used in the context of a full spectrum of treatment services, possibly including traditional 12-step fellowship-based treatments. Studies show also that naltrexone is effective when coupled with CBT. Patients receiving medical management with naltrexone, CBT, or both fared better on drinking outcomes [50].

Acamprosate

Acamprosate (Campral) is a synthetic compound that has a chemical structure similar to that of the naturally occurring amino acid neurotransmitters taurine and gamma-aminobutyric acid (GABA) [39]. Because chronic alcohol use is associated with decreased GABA and glutamate activity, a hyperexcitable glutamate system is one possible alcohol withdrawal mechanism. Glutamate systems may become unstable for 12 months after a person stops drinking. In a review of published, double-blind, placebo-controlled clinical trials evaluating the safety and efficacy of acamprosate in the treatment of alcohol use disorder, Mason reported that acamprosate appeared to improve treatment completion rate, abstinence rate and/or cumulative abstinence during treatment, and time to first drink, than placebo [53]. The effect on abstinence, combined with an excellent safety profile, lend support to the use of acamprosate across a broad range of patients with alcohol use disorder [54]. It is important to note that medication in combination with therapies can improve outcomes.

In July 2004, after many years of safe use in Europe and around the world, the FDA approved the use of acamprosate for the maintenance of alcohol abstinence [49]. As in the case of naltrexone, acamprosate reduces the reinforcing (pleasurable) effects of alcohol to reduce craving. Oral dosing is two 333-mg delayed-release tablets three times daily [39; 41]. Common side effects include diarrhea, anxiety, insomnia, nausea, dizziness, and weakness. Some research indicates that acamprosate may worsen depression and/or suicidal ideation; so, patients with a history of major depression should be monitored closely or prescribed a different medication [39]. Acamprosate is contraindicated in patients with severe renal impairment [39; 41]. Due to risk of diminished renal function in patients 65 years of age and older, baseline and frequent renal function tests should be performed in this population. Dose reductions also may be necessary [41].

Baclofen

Baclofen is a GABA agonist that may prove to be a unique therapeutic alternative to reduce alcohol craving and consumption. In a small, 12-week trial, patients with alcohol use disorder were given 10 mg of baclofen three times daily paired with motivational enhancement therapy. Patients experienced a reduction in number of drinks, drinking days, anxiety, and craving [55]. In a study of patients with alcohol use disorder and liver cirrhosis, baclofen was also found to work favorably in maintenance of alcohol abstinence. Seventy-one percent of baclofen-treated patients maintained abstinence as compared with 29% of the placebo group [56]. A 2018 meta-analysis of 12 randomized controlled trials that compared the efficacy of baclofen to placebo found that baclofen was associated with higher rates of abstinence than placebo but that its effects were not superior to placebo in increasing the number of abstinent days or in decreasing heavy drinking, craving, depression, or anxiety [57].

Anticonvulsants

Research has demonstrated that topiramate is efficacious in decreasing heavy drinking among individuals with alcohol use disorder [58]. In a controlled study, topiramate produced significant and meaningful improvement in a wide variety of drinking outcomes [59]. Topiramate may suppress the craving and rewarding effects of alcohol [60]. In a double-blind, controlled trial, 150 patients with alcohol use disorder were randomized to escalating doses of topiramate (25–300 mg/day) or placebo. Those on topiramate had a reduction in self-reported drinking (number of drinks and drinking days), alcohol craving, and plasma gamma-glutamyl transferase (an indicator of alcohol consumption) [61]. Side effects of topiramate include numbness in the extremities, fatigue, confusion, paresthesia, depression, change in taste, and weight loss. Use of topiramate for alcohol use disorder is off-label [39].

Carbamazepine has proven effective for treating acute alcohol withdrawal [62]. Its side effects include nausea, vomiting, drowsiness, dizziness, chest pain, headache, trouble urinating, numbness in extremities, liver damage, and allergic reaction [39]. In a 12-month, double-blind, placebo-controlled trial, 29 patients were assigned to carbamazepine three times daily (to reach an average blood level of 6 mg/liter) or placebo. Those treated with carbamazepine showed a delay in time to first drink and a decrease in number of drinks and drinking days [63].

Oxcarbazepine is a carbamazepine derivative, with fewer side effects and contraindications, used to prevent relapse in patients with alcohol use disorder by blocking alcohol withdrawal [62]. A group of 84 patients with alcohol use disorder following detoxification were randomized to 50 mg naltrexone, 1,500–1,800 mg oxcarbazepine, or 600–900 mg oxcarbazepine for 90 days. Approximately 58.6% of the high-dose oxcarbazepine patients remained alcohol-free, a significantly larger number as compared to the low-dose (42.8%) and naltrexone groups (40.7%) [64].

Opioid Use Disorder

Any treatment for opioid use disorder must take into consideration the chronic relapsing nature of opioid dependence, characterized by a variable course of relapse and remission in many patients. Treatments should emphasize patient motivation, psychoeducation, continuity of care, integration of pharmacotherapy and psychosocial support, and improved liaison between the treatment staff and the judicial system. Pharmacotherapy must be offered in a comprehensive healthcare context that also addresses the psychosocial aspects of dependence [65]. Patients with opioid use disorder frequently suffer from physical and psychiatric disorders, and targeted interventions of psychiatric comorbidity are essential in improving treatment outcome for these patients [65]. Polysubstance abuse is the rule rather than the exception in opioid use disorder, and concurrent use of other substances should be carefully monitored and treated when necessary [65]. Incarceration should never automatically result in discontinuation of an existing treatment; imprisonment offers a window of opportunity to initiate or restart treatment with a necessary continuation after release [65].

Crisis Intervention

In response to acute overdose, the short-acting opioid antagonist naloxone is considered the criterion standard. Naloxone is effective in reversing respiratory depression and coma in patients who have overdosed. There is no evidence that subcutaneous or intramuscular use is inferior to intravenous naloxone. This prompted discussion of making naloxone available to the general public for administration outside the healthcare setting to treat acute opioid overdose, and in 2014, the FDA approved naloxone as an autoinjector dosage form for home use by family members or caregivers [66]. The autoinjector delivers 0.4 mg naloxone intramuscularly or subcutaneously. The autoinjector comes with visual and voice instruction, including directions to seek emergency medical care after use [66]. In 2015, the FDA approved intranasal naloxone after a fast-track designation and priority review. Intranasal naloxone is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. It is available in a ready-to-use 2-mg, 4-mg, or 8-mg single-dose sprayer [67; 68; 69]. In 2023, the FDA approved 4-mg nasal spray naloxone for over-the-counter use [173].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the World Health Organization, people likely to witness an opioid overdose should have access to naloxone and be instructed in its administration to enable them to use it for the emergency management of suspected opioid overdose.

(https://www.who.int/publications/i/item/9789241548816. Last accessed April 27, 2023.)

Strength of Recommendation/Level of Evidence: Strong/very low

Harm Reduction

Harm reduction measures are primarily employed to minimize the morbidity and mortality from opioid abuse and to reduce public nuisance [2; 70]. As a part of this effort, measures to prevent and minimize the frequency and severity of overdoses have been identified. Enrollment in opioid substitution therapy, with agents such as methadone and buprenorphine, substantially reduces the risk of overdose as well as the risk for infection and other sequelae of illicit opioid use [2; 70].

Detoxification

The three primary treatment modalities used for detoxification are opioid agonists, non-opioid medications, and rapid and ultra-rapid opioid detoxification [71]. The most frequently employed method of opioid withdrawal is a slow, supervised detoxification during which an opioid agonist, usually methadone, is substituted for the abused opioid [72]. Methadone is the most frequently used opioid agonist due to the convenience of its once-a-day dosing [71]. Methadone is highly bound to plasma proteins and accumulates more readily than heroin in all body tissues. Methadone also has a longer half-life, approximately 22 hours, which makes withdrawal more difficult than from heroin. Substitution therapy with methadone has a high initial dropout rate (30% to 90%) and an early relapse rate. Alternative pharmacologic detoxification choices include clonidine (with or without methadone), midazolam, trazodone, or buprenorphine [72].

Many opioid withdrawal symptoms, such as restlessness, rhinorrhea, lacrimation, diaphoresis, myosis, piloerection, and cardiovascular changes, are mediated through increased sympathetic activation, the result of increased neuron activity in the locus coeruleus. Non-opioid agents (such as clonidine), which inhibit hyperactivation of noradrenergic pathways stemming from the locus coeruleus nucleus, have been used to manage acute withdrawal [72; 73]. The first non-opioid treatment approved for the management of opioid withdrawal symptoms is lofexidine [74]. In studies, patients treated with lofexidine reported less severe withdrawal symptoms and were more likely to complete treatment.

However, some withdrawal symptoms, including anxiety and myalgias, are resistant to clonidine; benzodiazepines and nonsteroidal anti-inflammatory drugs (NSAIDs) may be necessary to treat these symptoms. To mitigate withdrawal symptoms and assist in detoxification, alpha2-agonists, opioid agonist-antagonists, benzodiazepines, and antidepressants have been used [72].

Agonist Replacement Therapy

The goal of opioid replacement therapy is to reduce illicit drug use and associated health risks, with secondary goals of reducing unsafe sexual practices, improving vocational and psychosocial functioning, and enhancing quality of life [71]. The theoretical basis of opioid replacement stems from the finding that chronic opioid use results in an endogenous opioid deficiency as a result of the down-regulation of opioid production. This creates overwhelming cravings and necessitates interventions that shift the dependent patient's attention and drive from obsessive preoccupation with the next use of opioids to more adaptive areas of focus, such as work, relationships, and non-drug leisure activities [71].

For patients with opioid use disorder, the Department of Veterans Affairs Work Group recommends offering one of the following medications, considering patient preferences: buprenorphine/naloxone or methadone (in an opioid treatment program).

(https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPG.pdf. Last accessed April 27, 2023.)

Strength of Recommendation: Strong for

Methadone is now the most inexpensive and empirically validated agent available for use in opioid replacement therapy. Studies have shown one-year treatment retention rates of 80%, with significant reductions in illicit opioid use [71].

Treatment is initiated with a dose of 25–30 mg and is gradually titrated in 5- to 10-mg increments per day to a desired range of 60–120 mg. Low-dose treatment is associated with less positive outcomes than doses of 60–120 mg/day or greater [71; 75]. One published review of efficacy literature concluded that high doses of methadone (>50 mg daily) are more effective than low doses (<50 mg daily) in reducing illicit opioid use. This may be due to the increased availability of highly pure heroin [75]. Additionally, high doses of methadone are more effective than low doses of buprenorphine (<8 mg daily). High dosages of methadone are comparable to high dosages of buprenorphine (>8 mg daily) on measures of treatment retention and reduction of illicit opioid use [65]. Methadone is contraindicated for the following patients [73]:

- Those with known hypersensitivity to methadone hydrochloride
- Those experiencing respiratory depression
- Those with acute bronchial asthma or hypercapnia
- Those with known or suspected paralytic ileus

EVIDENCE-BASED PRACTICE RECOMMENDATION

When considering initiation of methadone, the American Pain Society recommends that clinicians perform an individualized medical and behavioral risk evaluation to assess risks and benefits of methadone, given methadone's specific pharmacologic properties and adverse effect profile.

(https://www.jpain.org/article/S1526-5900(14)00522-7/fulltext. Last accessed April 27, 2023.)

Strength of Recommendation/Level of Evidence: Strong/low

Buprenorphine offers several advantages over methadone, including lower cost, milder withdrawal symptoms following abrupt cessation, lower risk of overdose, and longer duration of action, allowing alternate-day dosing [71; 76]. Identifying subpopulations of opioid addicts who differentially respond to buprenorphine versus methadone has not been clearly established. However, patients with less chronic and less severe heroin dependence benefit more fully from buprenorphine than from a pure opioid agonist like methadone [71].

The transition to buprenorphine from long-acting opioids is difficult [77]. The ASAM warns that diversion and misuse are possible with buprenorphine, as is physical dependence. Respiratory depression may occur if buprenorphine is used with central nervous system depressants including alcohol, other opioids, and illicit drugs. Neonatal withdrawal has also been reported after use of buprenorphine during pregnancy. Buprenorphine is not recommended for patients with severe hepatic impairment [73].

Higher doses of buprenorphine (12 mg or greater) are more effective than lower doses in reducing illicit opioid use, with some studies reporting similar efficacy to methadone on major treatment-outcome measures. The primary advantage of buprenorphine over methadone is its superior safety profile [77].

Slow-release formulations of morphine that are effective with once-daily dosing are a viable alternative in the treatment of opioid dependence. These formulations considerably delay time to peak concentration after oral administration, resulting in delayed onset of action and making the reinforcing effects very weak when it is administered orally. Several trials have suggested that slow-release morphine has approximately equal efficacy with methadone; however, there is no definitive evidence of this effect [77; 78; 79]. Slow-release oral morphine may be a viable alternative for patients who are intolerant to methadone [80].

Tobacco Use Disorder

The first-line pharmacologic interventions for smoking cessation are nicotine-replacement therapy (NRT), bupropion, and varenicline [81; 82]. However, no pharmacotherapy has been approved for use among pregnant or nursing women.

Bupropion

Bupropion is an atypical antidepressant that has both dopaminergic and adrenergic actions [83]. In 1998, the slow-release preparation of bupropion became available as a prescription item specifically for smoking cessation, with the trade name Zyban. This treatment could be appropriate for smokers who do not wish to use an NRT or for those whose treatment with NRT has failed. Unlike NRT, smokers begin bupropion treatment one week prior to cessation. The suggested dosage is 300 mg/day, and the duration of treatment is 7 to 12 weeks [84]. A double-blind, placebo-controlled trial randomized patients to placebo or sustained-released bupropion (50 mg twice a day, 150 mg once a day, or 150 mg twice a day) and treated them for six weeks. Smokers with active depression were excluded, though smokers with a history of depression were not. The cessation rates at the end of therapy were 10.5%, 13.7%, 18.3%, and 24.4%, respectively. Follow-up at one year suggested a continued benefit of bupropion therapy [85]. Data from a study of bupropion combined with transdermal nicotine showed high long-term quit rates with the combination therapy [86]. Discontinuation of treatment may be appropriate for individuals unable to achieve significant progress after seven weeks, as success after this point is unlikely [39].

Varenicline Tartrate

Another effective non-nicotine therapy for smoking cessation is varenicline tartrate, a partial agonist selective for nicotine acetylcholine receptor subtypes. Released in 2006, varenicline is available in monthly dose packs (0.5 mg and 1 mg tablets) and is approved for a 12-week course of treatment [82]. Patients able to quit smoking may continue the therapy for an additional 12 weeks for increased likelihood of long-term cessation and even up to a year in certain cases, to prevent relapse; however, medication should be stopped and patients should be reassessed if the intervention has not led to smoking cessation within the initial 12 week timeframe [39; 87; 88]. Clinical trials reveal that varenicline may be favorable to bupropion for abstinence (44% versus 30%); the medication has also been shown to help at least 20% of patients remain smoke-free for up to one year [89; 90]. Recognizing that cessation success rates increase when pharmacologic and behavioral therapies are combined, the manufacturer urges patients to combine use of varenicline with a behavioral support plan. Co-administration of varenicline and transdermal nicotine may exacerbate incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue. One study found varenicline alone to be more effective than other treatment options, while a meta-analysis study found that combination therapy (varenicline and NRT) was more effective than varenicline alone [91; 92]. In 2021, the manufacturer of Chantix, a brand of varenicline, halted production of varenicline due to unacceptably high levels of nitrosamines; however, this issue was considered resolved by May 2022 [93]. In addition, all lots of 0.5-mg and 1-mg tablets of Chantix were subject to a voluntary recall. However, the FDA does not recommend that patients halt use of varenicline, and generic formulations and other brands remained available.

Other Options

The two second-line drugs for smoking cessation are clonidine and nortriptyline [81]. Clonidine is an antihypertensive medication that is administered orally or transdermally. It appears to increase the smoking cessation rate by approximately 11%; however, clonidine is known to produce such side effects as dry mouth, dizziness, sedation, and orthostatic hypotension [39; 94]. Clonidine has not been approved by the FDA for smoking cessation but has been used with individuals who have failed NRT or bupropion [39]. Nortriptyline is a tricyclic antidepressant that has been used to assist smoking cessation, although this is an unlabeled use [39]. A 12% improvement in cessation over controls has been reported, but the limited number of trials, combined with the adverse side effects (e.g., dry mouth, weight gain, constipation, drowsiness, sexual problems), makes nortriptyline a second-line intervention [81]. Several controlled trials have failed to show any benefit for either agent [39].

POLYSUBSTANCE USE

Despite the increased prevalence of individuals using multiple substances at the same time, limited research exists on evidence-based treatment practices that have demonstrated improved outcomes for individuals who use more than one substance [95]. Therefore, there is a need to identify and assess the effectiveness of treatment practices so that clinicians and organizations have the necessary resources and evidence-based practices to assist this population.

The Substance Abuse and Mental Health Services Administration (SAMHSA) has identified three evidence-based practices that engage and improve outcomes for individuals with concurrent substance use and concurrent substance use disorders [95]:

- FDA-approved pharmacotherapy together with counseling to treat:
  - Alcohol and cocaine dependence
  - Cocaine and opioid dependence
- Contingency management together with FDA-approved pharmacotherapy and counseling to treat:
  - Cocaine and opioid use and dependence
  - Cocaine dependence and alcohol and opioid use
- Twelve-step facilitation therapy together with FDA-approved pharmacotherapy and counseling to treat:
  - Cocaine and opioid dependence
  - Opioid and other substance dependence

CO-OCCURRING MENTAL DISORDERS

In the United States, 7.7 million adults have co-occurring mental and substance use disorders. Of the 20.3 million adults with substance use disorders, 37.9% also had mental illnesses. Among the 42.1 million adults with mental illness, 18.2% also had substance use disorders [96]. No specific combinations of mental and substance use disorders are defined uniquely as co-occurring disorders, but the most common mental disorders seen in substance use disorder treatment include [96]:

- Anxiety and mood disorders
- Schizophrenia
- Bipolar disorder
- Major depressive disorder
- Conduct disorders
- Post-traumatic stress disorder
- Attention deficit hyperactivity disorder (ADHD)

Patients with comorbid disorders demonstrate poorer treatment adherence and higher rates of treatment dropout than those without mental illness, which negatively affects outcomes [97]. Integrated treatment for comorbid drug use disorder and mental illness has been found to be consistently superior compared with separate treatment of each diagnosis. Integrated treatment of co-occurring disorders often involves using CBT strategies to boost interpersonal and coping skills and using approaches that support motivation and functional recovery.

Assessment

It is important to assess patients with substance use disorder for other psychiatric and substance use disorders. For example, alcohol and cocaine use disorders are frequent comorbidities in patients with opioid use disorder and can aggravate depressive symptoms [73; 99]. Bipolar illness is rare but has substantial treatment implications. Anxiety disorders frequently co-occur with depression, and traumatic experiences and post-traumatic stress disorder are common and should be thoroughly evaluated and treated [98; 99]. Independent disorders are psychiatric conditions occurring during periods of sustained abstinence or having an onset before the substance use disorder. A positive family history can aid in identifying an independent psychiatric disorder.

Comprehensive assessment tools can reduce the chance of a missed or incorrect diagnosis. Patients with psychiatric comorbidities often exhibit symptoms that are more persistent, severe, and resistant to treatment compared to patients who have either disorder alone [100; 101; 102; 103]. Assessment is critical to identify concomitant medical and psychiatric conditions that may need immediate attention and require transfer to a higher level of care [73]. The ASAM recommends that clinicians also assess social and environmental factors to identify facilitators and barriers to treatment, specifically to pharmacotherapy [73].

Treatment Approach

Treatment should initially focus on stabilization of the patient's substance use disorder, with an initial goal of two to four weeks abstinence before addressing comorbidities. Patients who persistently display symptoms of a psychiatric disorder during abstinence should be considered as having an independent disorder and should receive prompt psychiatric treatment [104].

Although depressive symptoms often improve following treatment admission, significant symptoms will persist in some patients [98]. Antidepressant medications can be effective in patients dually diagnosed with substance use disorder and depression when used at adequate doses for at least six weeks [105]. Factors emphasizing prompt antidepressant treatment include greater severity of depression, suicide risk, and co-occurring anxiety disorders [98].

Selective serotonin reuptake inhibitors (SSRIs) are generally safe and well-tolerated, but clinical trials with these agents in methadone patients have been negative [98]. Therefore, SSRIs may be considered first-line treatment based on their safety profile, but if the patient does not respond, then tricyclic antidepressants or newer generation agents should be considered. SSRIs in combination with CBT have been found to be highly effective for treating clients with comorbid depression [106]. More stimulating antidepressants, such as venlafaxine and bupropion, may be suitable in patients with prominent low energy or past or current symptoms consistent with ADHD [98].

The utility of nonpharmacologic treatments should be emphasized. Psychosocial therapies are as effective as pharmacotherapy in the treatment of mild-to-moderate depressive and anxiety symptoms. Treatment of personality disorders is nonpharmacologic [104]. If depression persists, psychosocial modalities, such as CBT, supportive therapy, or contingency management, have some evidence to support their efficacy in patients with substance use disorders [98; 106].

FACTORS IMPACTING RECOVERY

Stigma

Although substance use disorders affect millions of persons in the United States every year, stigma and shame surrounding these disorders remains. Although it is clear that substance use disorders are complex mental disorders, many continue to view it as a result of moral weakness and flawed character [107]. Experiences of this stigma, especially if expressed by a healthcare professional, can impede patients from seeking help or adhering to treatment.

Trauma

Various studies have found a disproportionately higher number of abuse, neglect, or trauma histories in patients with substance use disorders than in the general population [108; 109; 110; 111; 112]. Furthermore, substance abuse increases the likelihood of victimization, which can further promulgate the cycle of coping with trauma-related stress and self-medicating with addictive substances [113; 114; 115; 116; 117].

Some experts have asserted that traditional models of addiction recovery and relapse prevention do not consider the significant role that unresolved trauma can play in an addicted individual's attempt at recovery [118]. It is possible that traditional approaches tend to marginalize women more than their male counterparts and fail to sufficiently address the role that trauma has played in the development and maintenance of substance use disorder. An integrated, more holistic approach is needed to promote long-term recovery and prevent relapse [119].

Social Determinants of Health

Social determinants of health are the conditions in the environments where people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks. They can have a major impact on substance use disorder treatment and recovery. Examples of social determinants of health include [120]:

- Safe housing, transportation, and neighborhoods
- Racism, discrimination, and violence
- Education, job opportunities, and income
- Access to nutritious foods and physical activity opportunities
- Polluted air and water
- Language and literacy skills

Social determinants of health also contribute to wide health disparities and inequities. For example, people who lack reliable transportation are less likely to attend follow-up appointments or 12-step meetings, which raises the risk of relapse and treatment nonadherence [120].

LEGAL AND ETHICAL ISSUES IN THE TREATMENT OF SUBSTANCE USE DISORDERS

Federal statutes, regulations, and guidelines govern medications for opioid addiction. The SAMHSA's Division of Pharmacologic Therapies, part of SAMHSA's Center for Substance Abuse Treatment, manages the day-to-day oversight activities required to implement federal regulations surrounding the use medications approved by the FDA, such as methadone and buprenorphine for the treatment of opioid use disorder for practitioners and opioid treatment programs [121]. Some medications used to treat substance use disorder are controlled substances governed by the Controlled Substances Act.

Section 1262 of the Consolidated Appropriations Act of 2023 (also known as Omnibus bill), removes the federal requirement for practitioners to submit a Notice of Intent (i.e., have a DATA or X-waiver) to prescribe medications, like buprenorphine, for the treatment of opioid use disorder. All practitioners who have a current Drug Enforcement Administration (DEA) registration that includes Schedule III authority may now prescribe buprenorphine for opioid use disorder in their practice if permitted by applicable state law. This section also removes other federal requirements associated with the waiver, such as discipline restrictions, patient limits, and certification related to provision of counseling. Separately, section 1263 of the Consolidated Appropriations Act requires new or renewing DEA registrants, starting June 27, 2023, upon submission of their application, to have at least one of the following [122]:

- A total of eight hours of training from certain organizations on opioid or other substance use disorders for practitioners renewing or newly applying for a registration from the DEA to prescribe any Schedule II-V controlled medications
- Board certification in addiction medicine or addiction psychiatry from the American Board of Medical Specialties, American Board of Addiction Medicine, or the American Osteopathic Association

- Graduation within five years and status in good standing from medical, dental medicine, advanced practice nursing, or physician assistant school in the United States that included successful completion of an opioid or other substance use disorder curriculum of at least eight hours
- For dentists, the training may also include the safe pharmacologic management of dental pain and screening, brief intervention, and referral for appropriate treatment of patients with or at risk of developing opioid and other substance use disorders

Key ethical issues to consider when caring for patients with substance use disorders include informed consent, confidentiality, autonomy, competence, access to services, and explicit and implicit bias.

PAIN MANAGEMENT AND SUBSTANCE MISUSE

Persistent pain has been reported to affect one in three adults in the United States [123]. As such, a significant portion of persons with substance use disorders will have comorbid and sometimes chronic pain. There is no adequately validated instrument to differentiate pain patients who are at risk of dependence from those who are not. Research suggests that patients, even those with alcohol use disorder, with no history of opioid dependence are not at heightened risk of becoming addicted with short-term opioid exposure. However, those with a positive history of dependence would benefit from active recovery efforts while receiving such medications.

Despite the rise in prescription opioid analgesic use and misuse, definitive data on the rate of dependence among patients administered opioids for acute pain does not yet exist. There is, however, agreement on how to minimize the risk of iatrogenic dependence. These steps include screening for risk potential based on a family history of substance abuse and the exploration of different delivery systems that adequately treat pain but minimize abuse potential. Although a pattern of aberrant behavior may be grounds for caution, a history of opioid misuse does not necessarily preclude a patient from successful treatment with an opioid. Screening for psychologic disorders is also advisable, including psychosomatic causes of pain.

PAIN MANAGEMENT APPROACHES

Healthcare professionals should know the best clinical practices in opioid prescribing, including the associated risks of opioids, approaches to the assessment of pain and function, and pain management modalities. Pharmacologic and nonpharmacologic approaches should be used on the basis of current knowledge in the evidence base or best clinical practices. Patients with moderate-to-severe chronic pain who have been assessed and treated, over a period of time, with non-opioid therapy or nonpharmacologic pain therapy without adequate pain relief, are considered to be candidates for a trial of opioid therapy [124; 125; 127]. Initial treatment should always be considered individually determined and as a trial of therapy, not a definitive course of treatment [126].

The Centers for Disease Control and Prevention (CDC) originally published *Guideline for Prescribing Opioids for Chronic Pain—United States, 2016* in an effort to address an ongoing crisis of prescription opioid misuse, abuse, and overdose [125]. While these guidelines were based on the best available evidence at the time, there was some criticism that they were too focused on limiting opioid prescriptions—to the point of patients and prescribers complaining of stigma and reduced access to needed opioid analgesics. In response to this and to the availability of new evidence, the CDC published updates to the guideline in 2022 [127]. The updated clinical practice guideline is intended to achieve improved communication between clinicians and patients about the risks and benefits of pain treatment, including opioid therapy for pain; improved safety and effectiveness for pain treatment, resulting in improved function and quality of life for patients experiencing pain; and a reduction in the risks associated with long-term opioid therapy, including opioid use disorder, overdose, and death [127].

The 2022 clinical practice guideline includes 12 recommendations for clinicians who are prescribing opioids for outpatients 18 years of age or older with acute (duration <1 month) pain, subacute (duration of 1 to 3 months) pain, or chronic (duration of >3 months) pain outside of sickle cell disease related pain management, cancer pain treatment, palliative care, and end-of-life care. These recommendations are graded according to applicability and strength of the supporting evidence [127].

Acute Pain

Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids in a quantity no greater than that needed for the expected duration of severe pain. In most cases, three days or less will be sufficient; more than seven days will rarely be needed [125; 127]. However, it may be necessary to prescribe for longer periods in patients with acute severe pain. Approximately half of all states have passed legislation limiting initial opioid prescriptions for acute pain to a seven-day supply or less, and many insurers, pharmacy benefit managers, and pharmacies have enacted similar policies [127].

With postoperative, acute, or intermittent pain, analgesia often requires frequent titration, and the two- to four-hour analgesic duration with short-acting hydrocodone, morphine, and oxycodone is more effective than extended-release formulations. Short-acting opioids are also recommended in patients who are medically unstable or with highly variable pain intensity [128; 129; 130].

Chronic Pain

Nonpharmacologic therapy and non-opioid pharmacologic therapy are the preferred first-line therapies for chronic pain. Several nonpharmacologic approaches are therapeutic complements to pain-relieving medication, lessening the need for higher doses and perhaps minimizing side effects. These interventions can help decrease pain or distress that may be contributing to the pain sensation. Approaches include palliative radiotherapy, complementary/alternative methods, manipulative and body-based methods, and cognitive/behavioral techniques. The choice of a specific nonpharmacologic intervention is based on the patient's preference, which, in turn, is usually based on a successful experience in the past.

Implantable intrathecal opioid infusion and/or spinal cord stimulation may be options for severe, intractable pain. Both options require that devices or ports be implanted, with associated risks. With intrathecal opioid infusion, the ability to deliver the drug directly into the spine provides pain relief with significantly smaller opioid doses, which can help to minimize side effects (e.g., drowsiness, dizziness, dry mouth, nausea, vomiting, and constipation) that can accompany systemic pain medications that might be delivered orally, transdermally, or through an IV [131]. However, use of opioid infusion has traditionally been limited to cancer pain. With spinal cord stimulation therapy, the most challenging aspect is patient selection. In order for patients to be considered for spinal cord stimulation, other options should have been ineffective or be contraindicated. Spinal cord stimulation is indicated for severe neuropathic pain persisting at least six months.

If opioids are used, they should be combined with nonpharmacologic therapy and non-opioid pharmacologic therapy, as appropriate. Clinicians should consider opioid therapy only if expected benefits for pain and function are anticipated to outweigh risks to the patient [125; 127].

Opioid therapy for chronic pain should be presented as a trial for a pre-defined period (e.g., ≤30 days). The goals of treatment should be established with all patients prior to the initiation of opioid therapy, including reasonable improvements in pain, function, depression, anxiety, and avoidance of unnecessary or excessive medication use [125; 127; 132]. The treatment plan should describe therapy selection, measures of progress, and other diagnostic evaluations, consultations, referrals, and therapies.

In patients who are opioid-naïve, start at the lowest possible dose and titrate to effect. Dosages for patients who are opioid-tolerant should always be individualized and titrated by efficacy and tolerability [125; 127; 132]. When starting opioid therapy for chronic pain, clinicians should prescribe short-acting instead of extended-release/long-acting opioid formulations [125; 127].

The need for frequent progress and benefit/risk assessments during the trial should be included in patient education. Patients should also have full knowledge of the warning signs and symptoms of respiratory depression. Prescribers should carefully reassess evidence of benefits and risks when increasing the dosage to ≥50 mg morphine milligram equivalents (MME) per day. In its 2016 guideline, the CDC recommended that decisions to titrate dosage to ≥90 mg MME/day should be avoided or carefully justified [125; 133]. This recommendation does not appear in the 2022 revision [127].

Prescribers should be knowledgeable of federal and state opioid prescribing regulations. Issues of equianalgesic dosing, close patient monitoring during all dose changes, and cross-tolerance with opioid conversion should be considered. If necessary, treatment may be augmented, with preference for nonopioid and immediate-release opioids over long-acting/extended-release opioids. Taper opioid dose when no longer needed [134].

Palliative Care and Pain at the End of Life

Unrelieved pain is the greatest fear among people with a life-limiting disease, and the need for an increased understanding of effective pain management is well-documented [135]. Although experts have noted that 75% to 90% of end-of-life pain can be managed effectively, rates of pain are high, even among people receiving palliative care [135; 136; 137; 138].

The inadequate management of pain is the result of several factors related to both patients and clinicians. In a survey of oncologists, patient reluctance to take opioids or to report pain were two of the most important barriers to effective pain relief [139]. This reluctance is related to a variety of attitudes and beliefs [135; 139]:

- Fear of addiction to opioids
- Worry that if pain is treated early, there will be no options for treatment of future pain
- Anxiety about unpleasant side effects from pain medications
- Fear that increasing pain means that the disease is getting worse
- Desire to be a "good" patient
- Concern about the high cost of medications

Education and open communication are the keys to overcoming these barriers. Every member of the healthcare team should reinforce accurate information about pain management with patients and families. The clinician should initiate conversations about pain management, especially regarding the use of opioids, as few patients will raise the issue themselves or even express their concerns unless they are specifically asked [140]. It is important to acknowledge patients' fears individually and provide information to help them differentiate fact from fiction. For example, when discussing opioids with a patient who fears addiction, the clinician should explain that the risk of addiction is low [135]. It is also helpful to note the difference between addiction and physical dependence.

There are several other ways clinicians can allay patients' fears about pain medication:

- Assure patients that the availability of pain relievers cannot be exhausted; there will always be medications if pain becomes more severe.
- Acknowledge that side effects may occur but emphasize that they can be managed promptly and safely and that some side effects will abate over time.
- Explain that pain and severity of disease are not necessarily related.

Encouraging patients to be honest about pain and other symptoms is also vital. Clinicians should ensure that patients understand that pain is multidimensional and emphasize the importance of talking to a member of the healthcare team about possible causes of pain, such as emotional or spiritual distress. The healthcare team and patient should explore psychosocial and cultural factors that may affect self-reporting of pain, such as concern about the cost of medication.

Clinicians' attitudes, beliefs, and experiences also influence pain management, with addiction, tolerance, side effects, and regulations being the most important concerns [135; 137; 139; 141]. A lack of appropriate education and training in the assessment and management of pain has been noted to be a substantial contributor to ineffective pain management [139; 141]. As a result, many clinicians, especially primary care physicians, do not feel confident about their ability to manage pain in their patients [139; 141].

Clinicians require a clear understanding of available medications to relieve pain, including appropriate dosing, safety profiles, and side effects. If necessary, clinicians should consult with pain specialists to develop an effective approach.

Strong opioids are used for severe pain at the end of life [136; 137]. Morphine, buprenorphine, oxycodone, hydromorphone, fentanyl, and methadone are the most widely used in the United States [142]. Unlike nonopioids, opioids do not have a ceiling effect, and the dose can be titrated until pain is relieved or side effects become unmanageable. Patients who are opioid-naïve or who have been receiving low doses of a weak opioid, the initial dose should be low, and, if pain persists, the dose may be titrated up daily until pain is controlled.

More than one route of opioid administration will be needed by many patients during end-of-life care, but in general, opioids should be given orally, as this route is the most convenient and least expensive. The transdermal route is preferred to the parenteral route, although dosing with a transdermal patch is less flexible and so may not be appropriate for patients with unstable pain [137]. Intramuscular injections should be avoided because injections are painful, drug absorption is unreliable, and the time to peak concentration is long [137].

CREATING A TREATMENT PLAN AND ASSESSMENT OF ADDICTION RISK

Information obtained by patient history, physical examination, and interview, from family members, a spouse, or state prescription drug monitoring program (PDMP), and from the use of screening and assessment tools can help the clinician to stratify the patient according to level of risk for developing problematic opioid behavioral responses (***Table 3***) [143; 144]. Low-risk patients receive the standard level of monitoring, vigilance, and care. Moderate-risk patients should be considered for an additional level of monitoring and provider contact, and high-risk patients are likely to require intensive and structured monitoring and follow-up contact, additional consultation with psychiatric and addiction medicine specialists, and limited supplies of short-acting opioid formulations [125; 127; 145].

Before deciding to prescribe an opioid analgesic, clinicians should perform and document a detailed patient assessment that includes [132]:

- Pain indications for opioid therapy
- Nature and intensity of pain
- Past and current pain treatments and patient response
- Comorbid conditions
- Pain impact on physical and psychologic function
- Social support, housing, and employment
- Home environment (i.e., stressful or supportive)
- Pain impact on sleep, mood, work, relationships, leisure, and substance use
- Patient history of physical, emotional, or sexual abuse

RISK STRATIFICATION FOR PATIENTS PRESCRIBED OPIOIDS
Low Risk
Definable physical pathology with objective signs and reliable symptoms
Clinical correlation with diagnostic testing, including MRI, physical examination, and interventional diagnostic techniques
With or without mild psychologic comorbidity
With or without minor medical comorbidity
No or well-defined and controlled personal or family history of alcoholism or substance abuse
Age 45 years or older
High levels of pain acceptance and active coping strategies
High motivation and willingness to participate in multimodal therapy and attempting to function at normal levels
Medium Risk
Significant pain problems with objective signs and symptoms confirmed by radiologic evaluation, physical examination, or diagnostic interventions
Moderate psychologic problems, well controlled by therapy
Moderate coexisting medical disorders that are well controlled by medical therapy and are not affected by chronic opioid therapy (e.g., central sleep apnea)
Develops mild tolerance but not hyperalgesia without physical dependence or addiction
History of personal or family history of alcoholism or substance abuse
Pain involving more than three regions of the body
Defined pathology with moderate levels of pain acceptance and coping strategies
Willing to participate in multimodal therapy, attempting to function in normal daily life
High Risk
Widespread pain without objective signs and symptoms
Pain involving more than three regions of the body
Aberrant drug-related behavior
History of alcoholism or drug misuse, abuse, addiction, diversion, dependency, tolerance, or hyperalgesia
Major psychologic disorders
Age younger than 45 years
HIV-related pain
High levels of pain exacerbation and low levels of coping strategies
Unwilling to participate in multimodal therapy, not functioning close to a near normal lifestyle
HIV = human immunodeficiency syndrome, MRI = magnetic resonance imaging.
Source: [143; 144] *Table 3*

If substance abuse is active, in remission, or in the patient's history, consult an addiction specialist before starting opioids [132]. In active substance abuse, do not prescribe opioids until the patient is engaged in treatment/recovery program or other arrangement made, such as addiction professional co-management and additional monitoring. When considering an opioid analgesic (particularly those that are extended-release or long-acting), one must always weigh the benefits against the risks of overdose, abuse, addiction, physical dependence and tolerance, adverse drug interactions, and accidental exposure by children [125; 127; 134].

Screening and assessment tools can help guide patient stratification according to risk level and inform the appropriate degree of structure and monitoring in the treatment plan. It should be noted that despite widespread endorsement of screening tools used to help determine patient risk level, most tools have not been extensively evaluated, validated, or compared to each other, and evidence of their reliability is poor [143; 144].

Risk Assessment Tools

Opioid Risk Tool (ORT)

The Opioid Risk Tool (ORT) is a five-item, patient-administered assessment to help predict aberrant drug-related behavior. The ORT is also used to establish patient risk level through categorization into low, medium, or high levels of risk for aberrant drug-related behaviors based on responses to questions of previous alcohol/drug abuse, psychologic disorders, and other risk factors [146].

Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R)

The Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) is a patient-administered, 24-item screen with questions addressing history of alcohol/substance use, psychologic status, mood, cravings, and stress. Like the ORT, the SOAPP-R helps assess risk level of aberrant drug-related behaviors and the appropriate extent of monitoring [146; 147].

Screening Instrument or Substance Abuse Potential (SISAP)

The Screening Instrument or Substance Abuse Potential (SISAP) tool is a self-administered, five-item questionnaire addressing history developed used to predict the risk of opioid misuse. The SISAP is used to identify patients with a history of alcohol/substance abuse and improve pain management by facilitating focus on the appropriate use of opioid analgesics and therapeutic outcomes in the majority of patients who are not at risk of opioid abuse, while carefully monitoring those who may be at greater risk [146].

CAGE and CAGE-AID

The original CAGE (Cut down, Annoyed, Guilty, and Eye-opener) Questionnaire consisted of four questions designed to help clinicians determine the likelihood that a patient was misusing or abusing alcohol. These same four questions were modified to create the CAGE-AID (adapted to include drugs), revised to assess the likelihood of current substance abuse [148].

Diagnosis, Intractability, Risk, and Efficacy (DIRE) Score

The Diagnosis, Intractability, Risk, and Efficacy (DIRE) risk assessment score is a clinician-rated questionnaire that is used to predict patient compliance with long-term opioid therapy [146; 149]. Patients scoring lower on the DIRE tool are poor candidates for long-term opioid analgesia.

Considerations for Pain Management in Patients with Comorbid Opioid Use Disorder

Although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. Clinicians should use nonpharmacologic and nonopioid pharmacologic pain treatments as appropriate to provide optimal pain management [150]. For patients with pain who have an active opioid use disorder but are not in treatment, clinicians should consider buprenorphine or methadone treatment for opioid use disorder, which can also help with concurrent management of pain [150]. For patients who are treated with buprenorphine for opioid use disorder and experience acute pain, clinicians can consider temporarily increasing the buprenorphine dosing frequency (e.g., to twice a day) to help manage pain, given the duration of effects of buprenorphine is shorter for pain than for suppression of withdrawal [150; 151]. For severe acute pain (e.g., from trauma or unplanned major surgery) in patients receiving buprenorphine for opioid use disorder, clinicians can consider additional as-needed doses of buprenorphine. In supervised

settings, adding a short-acting full agonist opioid to the patient's regular dosage of buprenorphine can be considered without discontinuing the patient's regular buprenorphine dosage; however, if a decision is made to discontinue buprenorphine to allow for more mu-opioid receptor availability, patients should be monitored closely because high doses of a full agonist opioid might be required, potentially leading to oversedation and respiratory depression as buprenorphine's partial agonist effect lessens. For patients receiving naltrexone for opioid use disorder, short-term use of higher-potency nonopioid analgesics (e.g., NSAIDs) can be considered to manage severe acute pain. Patients receiving methadone for opioid use disorder who require additional opioids as treatment for severe acute pain management should be carefully monitored, and when feasible should optimally be treated by a clinician experienced in the treatment of pain in consultation with their opioid treatment program [150]. The *ASAM National Practice Guideline for the Treatment of Opioid Use Disorder (2020 Focused Update)* provides additional recommendations for the management of patients receiving medications for opioid use disorder who have planned surgeries for which nonopioid therapies are not anticipated to provide sufficient pain relief [150].

Informed Consent and Treatment Agreements

The initial opioid prescription is preceded by a written informed consent or "treatment agreement" [132]. This agreement should address potential side effects, tolerance and/or physical dependence, drug interactions, motor skill impairment, limited evidence of long-term benefit, misuse, dependence, addiction, and overdose. Informed consent documents should include information regarding the risk/benefit profile for the drug(s) being prescribed. The prescribing policies should be clearly delineated, including the number/frequency of refills, early refills, and procedures for lost or stolen medications. The treatment agreement also outlines joint physician and patient responsibilities. The patient agrees to using medications safely, refraining from "doctor shopping," and consenting to routine urine drug testing (UDT). The prescriber's responsibility is to address unforeseen problems and prescribe scheduled refills. Reasons for opioid therapy change or discontinuation should be listed. Agreements can also include sections related to follow-up visits, monitoring, and safe storage and disposal of unused drugs.

Periodic Review and Monitoring

When implementing a chronic pain treatment plan that involves the use of opioids, the patient should be frequently reassessed for changes in pain origin, health, and function [132]. This can include input from family members and/or the state PDMP. During the initiation phase and during any changes to the dosage or agent used, patient contact should be increased. At every visit, chronic opioid response may be monitored according to the "5 A's" [132; 152]:

- Analgesia
- Activities of daily living
- Adverse or side effects
- Aberrant drug-related behaviors
- Affect (i.e., patient mood)

Signs and symptoms that, if present, may suggest a problematic response to the opioid and interference with the goal of functional improvement include [153; 154]:

- Excessive sleeping or days and nights turned around
- Diminished appetite
- Short attention span or inability to concentrate
- Mood volatility, especially irritability
- Lack of involvement with others
- Impaired functioning due to drug effects
- Use of the opioid to regress instead of re-engaging in life
- Lack of attention to hygiene and appearance

The decision to continue, change, or terminate opioid therapy is based on progress toward treatment objectives and absence of adverse effects and risks of overdose or diversion [132]. Satisfactory therapy is indicated by improvements in pain, function, and quality of life. Brief assessment tools to assess pain and function may be useful, as may UDTs. Treatment plans may include periodic pill counts to confirm adherence and minimize diversion.

Involvement of Family

Family members of the patient can provide the clinician with valuable information that better informs decision making regarding continuing opioid therapy. Family members can observe whether a patient is losing control of his or her life or becoming less functional or more depressed during the course of opioid therapy. They can also provide input regarding positive or negative changes in patient function, attitude, and level of comfort. The following questions can be asked of family members or a spouse to help clarify whether the patient's response to opioid therapy is favorable or unfavorable [153; 154]:

- Is the person's day centered around taking the opioid medication? Response can help clarify long-term risks and benefits of the medication and identify other treatment options.
- Does the person take pain medication only on occasion, perhaps three or four times per week? If yes, the likelihood of addiction is low.
- Have there been any other substance (alcohol or drug) abuse problems in the person's life? An affirmative response should be taken into consideration when prescribing.
- Does the person in pain spend most of the day resting, avoiding activity, or feeling depressed? If so, this suggests the pain medication is failing to promote rehabilitation. Daily activity is essential, and the patient may be considered for enrollment in a graduated exercise program.
- Is the person in pain able to function (e.g., work, do household chores, play) with pain medication in a way that is clearly better than without? If yes, this suggests the pain medication is contributing to wellness.

Assessment Tools

VIGIL is the acronym for a five-step risk management strategy designed to empower clinicians to appropriately prescribe opioids for pain by reducing regulatory concerns and to give pharmacists a framework for resolving ambiguous opioid analgesic prescriptions in a manner that preserves legitimate patient need while potentially deterring diverters. The components of VIGIL are:

- Verification: Is this a responsible opioid user?
- Identification: Is the identity of this patient verifiable?
- Generalization: Do we agree on mutual responsibilities and expectations?
- Interpretation: Do I feel comfortable allowing this person to have controlled substances?
- Legalization: Am I acting legally and responsibly?

The foundation of VIGIL is a collaborative physician/pharmacist relationship [155].

The Current Opioid Misuse Measure (COMM) is a 17-item patient self-report assessment designed to help clinicians identify misuse or abuse in patients being treated for chronic pain. Unlike the ORT and the SOAPP-R, the COMM identifies aberrant behaviors associated with opioid misuse in patients already receiving long-term opioid therapy [145]. Sample questions include: In the past 30 days, how often have you had to take more of your medication than prescribed? In the past 30 days, how much of your time was spent thinking about opioid medications (e.g., having enough, taking them, dosing schedule)?

PATIENT RISK LEVEL AND FREQUENCY OF MONITORING			
Monitoring Tool	**Patient Risk Level**		
	Low	**Medium**	**High**
Urine drug test	Every 1 to 2 years	Every 6 to 12 months	Every 3 to 6 months
State prescription drug monitoring program	Twice per year	Three times per year	Four times per year

Source: [158] *Table 4*

Guidelines by the CDC, the Federation of State Medical Boards (FSMB), and the Joint Commission stress the importance of documentation from both a healthcare quality and medicolegal perspective. Research has found widespread deficits in chart notes and progress documentation with patients with chronic pain receiving opioid therapy, and the Pain Assessment and Documentation Tool (PADT) was designed to address these shortcomings [156]. The PADT is a clinician-directed interview, with most sections (e.g., analgesia, activities of daily living, adverse events) consisting of questions asked of the patient. However, the potential aberrant drug-related behavior section must be completed by the physician based on his or her observations of the patient.

The Brief Intervention Tool is a 26-item, "yes-no," patient-administered questionnaire used to identify early signs of opioid abuse or addiction. The items assess the extent of problems related to drug use in several areas, including drug use-related functional impairment [157].

Urine Drug Tests

UDTs may be used to monitor adherence to the prescribed treatment plan and to detect unsanctioned drug use. They should be used more often in patients receiving addiction therapy, but clinical judgment is the ultimate guide to testing frequency (***Table 4***) [158]. The CDC recommends clinicians should use UDT before starting opioid therapy and consider UDT at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs [125; 127]. However, this recommendation was based on low-quality evidence that indicates little confidence in the effect estimate.

Initially, testing involves the use of class-specific immunoassay drug panels [132]. If necessary, this may be followed with gas chromatography/mass spectrometry for specific drug or metabolite detection. It is important that testing identifies the specific drug rather than the drug class, and the prescribed opioid should be included in the screen. Any abnormalities should be confirmed with a laboratory toxicologist or clinical pathologist. Immunoassay may be used point-of-care for "on-the-spot" therapy changes, but the high error rate prevents its use in major clinical decisions except with liquid chromatography coupled to tandem mass spectrometry confirmation.

Urine test results suggesting opioid misuse should be discussed with the patient using a positive, supportive approach. The test results and the patient discussion should be documented.

Concurrent Use of Benzodiazepines

In 2019, 16% of persons who died of an opioid overdose also tested positive for benzodiazepines, a class of sedative medication commonly prescribed for anxiety, insomnia, panic attack, and muscle spasm [159]. Benzodiazepines work by raising the level of GABA in the brain. Common formulations include diazepam, alprazolam, and clonazepam. Combining benzodiazepines with opioids is unsafe because both classes of drug cause central nervous system depression and sedation and can decrease respiratory drive—the usual cause of overdose fatality. Both classes have the potential for drug dependence and addiction.

The CDC recommends that healthcare providers use particular caution prescribing benzodiazepines concurrently with opioids [125; 127]. If a benzodiazepine is to be discontinued, the clinician should taper the medication gradually, because abrupt withdrawal can lead to rebound anxiety and complications such as hallucinations, seizures, delirium tremens, and, in rare instances, death. A commonly used tapering schedule is a reduction of the benzodiazepine dose by 25% every one to two weeks [125; 127].

Consultation and Referral

It is important to seek consultation or patient referral when input or care from a pain, psychiatry, addiction, or mental health specialist is necessary. Clinicians who prescribe opioids should become familiar with opioid addiction treatment options (including licensed opioid treatment programs for methadone and office-based opioid treatment for buprenorphine) if referral is needed [132].

Ideally, providers should be able to refer patients with active substance abuse who require pain treatment to an addiction professional or specialized program. In reality, these specialized resources are scarce or non-existent in many areas [132]. Therefore, each provider will need to decide whether the risks of continuing opioid treatment while a patient is using illicit drugs outweigh the benefits to the patient in terms of pain control and improved function [160].

Medical Records

As noted, documentation is a necessary aspect of all patient care, but it is of particular importance when opioid prescribing is involved. All clinicians should maintain accurate, complete, and up-to-date medical records, including all written or telephoned prescription orders for opioid analgesics and other controlled substances, all written instructions to the patient for medication use, and the name, telephone number, and address of the patient's pharmacy [132]. Good medical records demonstrate that a service was provided to the patient and that the service was medically necessary. Regardless of the treatment outcome, thorough medical records protect the prescriber.

Patient Education on the Use and Disposal of Opioids

Patients and caregivers should be counseled regarding the safe use and disposal of opioids. As part of its mandatory Risk Evaluation and Mitigation Strategy (REMS) for extended-release/long-acting opioids, the FDA has developed a patient counseling document with information on the patient's specific medications, instructions for emergency situations and incomplete pain control, and warnings not to share medications or take them unprescribed [134]. A copy of this form may be accessed online at https://www.fda.gov/media/114694/download.

When prescribing opioids, clinicians should provide patients with the following information [134]:

- Product-specific information
- Taking the opioid as prescribed
- Importance of dosing regimen adherence, managing missed doses, and prescriber contact if pain is not controlled
- Warning and rationale to never break or chew/crush tablets or cut or tear patches prior to use
- Warning and rationale to avoid other central nervous system depressants, such as sedative-hypnotics, anxiolytics, alcohol, or illicit drugs
- Warning not to abruptly halt or reduce the opioid without physician oversight of safe tapering when discontinuing
- The potential of serious side effects or death
- Risk factors, signs, and symptoms of overdose and opioid-induced respiratory depression, gastrointestinal obstruction, and allergic reactions
- The risks of falls, using heavy machinery, and driving
- Warning and rationale to never share an opioid analgesic
- Rationale for secure opioid storage
- Warning to protect opioids from theft
- Instructions for disposal of unneeded opioids, based on product-specific disposal information

There are no universal recommendations for the proper disposal of unused opioids, and patients are rarely advised of what to do with unused or expired medications [161]. According to the FDA, most medications that are no longer necessary or have expired should be removed from their containers, mixed with undesirable substances (e.g., cat litter, used coffee grounds), and put into an impermeable, nondescript container (e.g., disposable container with a lid or a sealed bag) before throwing in the trash [162]. Any personal information should be obscured or destroyed. The FDA recommends that certain medications, including oxycodone/acetaminophen (Percocet), oxycodone (OxyContin tablets), and transdermal fentanyl (Duragesic Transdermal System), be flushed down the toilet instead of thrown in the trash [162; 163]. The FDA provides a free toolkit of materials (e.g., social media images, fact sheets, posters) to raise awareness of the serious dangers of keeping unused opioid pain medicines in the home and with information about safe disposal of these medicines. The Remove the Risk Outreach toolkit is updated regularly and can be found at https://www.fda.gov/drugs/ensuring-safe-use-medicine/safe-opioid-disposal-remove-risk-outreach-toolkit [163]. Patients should be advised to flush prescription drugs down the toilet only if the label or accompanying patient information specifically instructs doing so.

The American College of Preventive Medicine has established best practices to avoid diversion of unused drugs and educate patients regarding drug disposal [161]:

- Consider writing prescriptions in smaller amounts.
- Educate patients about safe storing and disposal practices.
- Give drug-specific information to patients about the temperature at which they should store their medications. Generally, the bathroom is not the best storage place. It is damp and moist, potentially resulting in potency decrements, and accessible to many people, including children and teens, resulting in potential theft or safety issues.
- Ask patients not to advertise that they are taking these types of medications and to keep their medications secure.
- Refer patients to community "take back" services overseen by law enforcement that collect controlled substances, seal them in plastic bags, and store them in a secure location until they can be incinerated. Contact your state law enforcement agency or visit https://www.dea.gov to determine if a program is available in your area.

Discontinuing Opioid Therapy

The decision to continue or end opioid prescribing should be based on a physician-patient discussion of the anticipated benefits and risks. An opioid should be discontinued with resolution of the pain condition, intolerable side effects, inadequate analgesia, lack of improvement in quality of life despite dose titration, deteriorating function, or significant aberrant medication use [125; 127; 132].

Clinicians should provide patients physically dependent on opioids with a safely structured tapering protocol. Withdrawal is managed by the prescribing physician or referral to an addiction specialist. Patients should be reassured that opioid discontinuation is not the end of treatment; continuation of pain management will be undertaken with other modalities through direct care or referral.

As a side note, cannabis use by patients with chronic pain receiving opioid therapy has traditionally been viewed as a treatment agreement violation that is grounds for termination of opioid therapy. However, some now argue against cannabis use as a rationale for termination or substantial treatment and monitoring changes, especially considering the increasing legalization of medical use at the state level [160].

Considerations for Non-English-Proficient Patients

For patients who are not proficient in English, it is important that information regarding the risks associated with the use of opioids and available resources be provided in their native language, if possible.

When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter. In any case in which information regarding treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered. Print materials are also available in many languages, and these should be offered whenever necessary.

IDENTIFICATION OF DRUG DIVERSION/SEEKING BEHAVIORS

Research has more closely defined the location of prescribed opioid diversion into illicit use in the supply chain from the manufacturer to the distributor, retailer, and the end user (the pain patient). This information carries with it substantial public policy and regulatory implications. The 2021 National Survey on Drug Use and Health asked non-medical users of prescription opioids how they obtained their most recently used drugs [2]. Among persons 12 years of age or older, 39.3% obtained their prescription opioids through a prescription from one doctor (vs. 34.7% in 2019), 33.9% got them from a friend or relative for free, 7.9% bought from a drug dealer or other stranger, and 7.3% bought them from a friend or relative [2]. Less frequent sources included stealing from a friend or relative (3.7%); multiple doctors (3.2%); and theft from a doctor's office, clinic, hospital, or pharmacy (0.7%) (vs. 0.2% in 2009–2010) [2].

As discussed, UDTs can give insight into patients who are misusing opioids. A random sample of UDT results from 800 patients treated for pain at a Veterans Affairs facility found that 25.2% were negative for the prescribed opioid while 19.5% were positive for an illicit drug/unreported opioid [164]. Negative UDT results for the prescribed opioid do not necessarily indicate diversion, but may indicate the patient halted his/her use due to side effects, lack of efficacy, or pain remission. The concern arises over the increasingly stringent climate surrounding clinical decision-making regarding aberrant UDT results and that a negative result for the prescribed opioid or a positive UDT may serve as the pretense to terminate a patient rather than guide him/her into addiction treatment or an alternative pain management program [165].

In addition to aberrant urine screens, there are certain behaviors that are suggestive of an emerging opioid use disorder. The most suggestive behaviors are [160; 166; 167]:

- Selling medications
- Prescription forgery or alteration
- Injecting medications meant for oral use
- Obtaining medications from nonmedical sources
- Resisting medication change despite worsening function or significant negative effects
- Loss of control over alcohol use
- Using illegal drugs or non-prescribed controlled substances
- Recurrent episodes of:
  - Prescription loss or theft
  - Obtaining opioids from other providers in violation of a treatment agreement
  - Unsanctioned dose escalation
  - Running out of medication and requesting early refills

Behaviors with a lower level of evidence for their association with opioid misuse include [160; 166; 167]:

- Aggressive demands for more drug
- Asking for specific medications
- Stockpiling medications during times when pain is less severe
- Using pain medications to treat other symptoms

- Reluctance to decrease opioid dosing once stable
- In the earlier stages of treatment:
  - Increasing medication dosing without provider permission
  - Obtaining prescriptions from sources other than the pain provider
  - Sharing or borrowing similar medications from friends/family

The Institute for Clinical Systems Improvement recommends considering screening patients for substance use disorders when there is an unclear etiology of pain.

(https://www.icsi.org/wp-content/uploads/2019/10/Pain-Interactive-7th-V2-Ed-8.17.pdf. Last accessed April 27, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

INTERVENTIONS FOR SUSPECTED OR KNOWN ADDICTION OR DRUG DIVERSION

There are a number of actions that prescribers and dispensers can take to prevent or intervene in cases of drug diversion. These actions can be generally categorized based on the various mechanisms of drug diversion.

Prevention is the best approach to addressing drug diversion. As noted, the most common source of nonmedical use of prescribed opioids is from a family member or friend, through sharing, buying, or stealing. To avoid drug sharing among patients, healthcare professionals should educate patients on the dangers of sharing opioids and stress that "doing prescription drugs" is the same as "using street drugs" [161]. In addition, patients should be aware of the many options available to treat chronic pain aside from opioids. To prevent theft, patients should be advised to keep medications in a private place and to refrain from telling others about the medications being used.

Communication among providers and pharmacies can help to avoid inappropriate attainment of prescription drugs through "doctor shopping." Prescribers should keep complete and up-to-date records for all controlled substance prescribing. When possible, electronic medical records should be integrated between pharmacies, hospitals, and managed care organizations [161]. If available, it is also best practice to periodically request a report from the state's prescription reporting program to evaluate the prescribing of opioids to your patients by other providers [161].

When dealing with patients suspected of drug seeking/diversion, first inquire about prescription, over-the-counter, and illicit drug use and perform a thorough examination [161]. Pill counting and/or UDT may be necessary to investigate possible drug misuse. Photo identification or other form of identification and social security number may be required prior to dispensing the drug, with proof of identity documented fully. If a patient is displaying suspicious behaviors, consider prescribing for limited quantities.

If a patient is found to be abusing prescribed opioids, this is considered a violation of the treatment agreement and the clinician must make the decision whether or not to continue the therapeutic relationship. If the relationship is terminated, it must be done ethically and legally. The most significant issue is the risk of patient abandonment, which is defined as ending a relationship with a patient without consideration of continuity of care and without providing notice to the patient. The American Medical Association Code of Ethics states that physicians have an obligation to support continuity of care for their patients. While physicians have the option of withdrawing from a case, they should notify the patient (or authorized decision maker) long enough in advance to permit the patient to secure another physician and facilitate transfer of care when appropriate [168]. Patients may also be given resources and/or recommendations to help them locate a new clinician.

Patients with chronic pain found to have an ongoing substance abuse problem or addiction should be referred to a pain specialist for continued treatment. Theft or loss of controlled substances is reported to the DEA. If drug diversion has occurred, the activity should be documented and a report to law enforcement should be made [169].

COMPLIANCE WITH STATE AND FEDERAL LAWS

In response to the rising incidence in prescription opioid abuse, addiction, diversion, and overdose since the late 1990s, the FDA has mandated opioid-specific REMS to reduce the potential negative patient and societal effects of prescribed opioids. Other elements of opioid risk mitigation include FDA partnering with other governmental agencies, state professional licensing boards, and societies of healthcare professionals to help improve prescriber knowledge of appropriate and safe opioid prescribing and safe home storage and disposal of unused medication [153].

Several regulations and programs at the state level have been enacted in an effort to reduce prescription opioid abuse, diversion, and overdose, including [170]:

- Physical examination required prior to prescribing
- Tamper-resistant prescription forms
- Pain clinic regulatory oversight
- Prescription limits
- Prohibition from obtaining controlled substance prescriptions from multiple providers
- Patient identification required before dispensing
- Immunity from prosecution or mitigation at sentencing for individuals seeking assistance during an overdose

Controlled Substances Laws/Rules

The DEA is responsible for formulating federal standards for the handling of controlled substances. In 2011, the DEA began requiring every state to implement electronic databases that track prescribing habits, referred to as PDMPs. Specific policies regarding controlled substances are administered at the state level [171].

According to the DEA, drugs, substances, and certain chemicals used to make drugs are classified into five distinct categories or schedules depending upon the drug's acceptable medical use and the drug's abuse or dependency potential [172]. The abuse rate is a determinate factor in the scheduling of the drug; for example, Schedule I drugs are considered the most dangerous class of drugs with a high potential for abuse and potentially severe psychologic and/or physical dependence.

State-Specific Laws and Rules

Most states have established laws and rules governing the prescribing and dispensing of opioid analgesics. It is each prescriber's responsibility to have knowledge of and adhere to the laws and rules of the state in which he or she prescribes.

CONCLUSION

Substance use disorders are associated with serious morbidity and mortality, and advances in the understanding of these disorders have led to the development of effective treatments. More recently, the abuse of prescription opioids has become considerably more widespread, fueled in part by the availability of such drugs over the Internet. Medical, mental health, and other healthcare professionals in a variety of settings may encounter patients with comorbid substance use disorders and pain. The knowledge gained from the contents of this course can greatly assist the healthcare professional in identifying, treating, and providing an appropriate referral to patients with substance use disorders while also addressing pain management needs.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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