Absolute Addiction Psychiatry Review

An Essential Board Exam Study Guide

Carla Marienfeld
Editor

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Part I

Introduction, Evaluation, Treatment

Health Services for Addiction Treatment and Levels of Care

1

Howard B. Moss

High-Yield Review Points

- Addiction is best addressed as a chronic disease.
- Addiction treatment is provided along a continuum or levels of care.
- The multidimensional assessment is fundamental to the clinical matching of patients to therapeutic services.
- Successful addiction treatment should address patient engagement and retention.
- Fiscal and resource management is now an essential aspect of addiction treatment delivery.
- Patient placement criteria for defined levels of care for addictive disorders have been developed by the American Society of Addiction Medicine (ASAM).
  - These criteria are now accepted by government agencies and commercial insurers in authorizing and paying for treatment.
- Treatment congruence with quality performance measures is likely to influence the future delivery of addiction treatment.

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Introduction

The Complexity of Health Services for Persons with Addictive Disorders

The status of the health services environment is central to the daily work of the addiction psychiatrist. It is about where we work, who our patients are, how we evaluate our patients, how our patients pay for our services, and how we get compensated for the work we do. All of this occurs within our political, technological, and sociocultural environment. Move from your town, city, county, state, or country to another venue, and the health services environment can be radically different. Likewise, moving to and from an academic medical center, a group practice, a community clinic, a veteran's hospital, or a private office will change the parameters of the health services you are providing. The diligent addiction psychiatrist needs to be aware and understand these complexities of care to best provide quality services to our patients.

What do we mean by health services? Health services are the multidisciplinary factors such as treatment models, social factors, financing systems, organizational structures and processes, health technologies, and personal behaviors that affect access to healthcare, as well as the quality and cost of healthcare, and ultimately, a patient's health and well-being. Health services for addictive disorders have changed substantially over the last 15 years. We have new treatments, new public policies, new organizational structures, new technologies, new social perceptions of our patients, new approaches to the funding of care, and new perspectives on the disorders we treat. It's a dynamic process requiring our ongoing attention and efforts to broaden research of evidence-based practices and then educating and empowering providers to feel more confi dent in treating substance use disorders.

Health services research in addiction treatment: Health services research drives many of the policies and procedures in addiction treatment at the federal, state, and local level. This applied health services research provides data, evidence, and tools to make addiction treatment affordable, safe, effective, equitable, accessible, and patient-centered. For example, products stemming from addiction health services research serve to enable providers and patients to make better clinical decisions regarding treatment options, as well as informing public policy.

Key Concepts that Influence the Current Best Practices Treatment Models for Addictive Disorders

Addiction: According to the American Society of Addiction Medicine, addiction is a primary, chronic, disease of brain reward, motivation, memory, and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social, and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.

Addiction as a chronic disease: In the past, physicians, policymakers, patients, and families have supposed that patients entering addiction treatment should be cured and able to maintain lifelong abstinence following a single episode of specialized treatment. When a single episode is ineffective, it is not unusual for these same individuals to become discouraged when a relapse occurs. Yet, Dennis and others [1] have shown that more than half the patients entering publicly funded addiction programs require multiple episodes of treatment over several years to achieve and sustain recovery. The clinical course of many patients is marked by cycles of recovery, relapse, and repeated treatments, which may span many years before resulting in long-term recovery. The presence of co-occurring disorders further complicates the picture. Patients who have co-occurring disorders are more likely to experience difficulties with treatment and medication adherence, and they experience shorter treatment episodes or leave treatment against medical advice. In addition, patients may be administratively discharged, experience compromised functional status, have difficulties adjusting to their communities, or have reduced quality of life resulting in poor outcomes [1]. Thus, it has become increasingly clear that addiction should be viewed as a chronic, rather than acute condition, and that the treating addiction psychiatrist, particularly when managing patients with significant psychiatric comorbidity, needs to appreciate the cyclical nature of the disorder, its chronicity, and maintain appropriate expectations and resources. The contemporary perspective is to view substance use disorders more like chronic diseases such as hypertension or diabetes rather than acute conditions like pneumonia [2]. New models of addiction treatment now accommodate the natural history of the disorder, and policy makers are beginning to follow suit, allowing for better treatment outcomes.

The continuum of care: The concept of a continuum of care has been applied as a central concept in the management of a wide variety of disorders and conditions that require caregiving. The World Health Organization defines the continuum of care having two dimensions: first, there is the timing of care giving and second, there is the place and approach to care giving. For maximum health benefit, these two dimensions are best linked and integrated into what we would call "levels of care." In addiction treatment, the "continuum of care" is interpreted as a fluid treatment system in which patients initially enter treatment at a level appropriate to their clinical needs, and then step up to more intensive treatment or down to less intense treatment as clinically indicated. For example, patients may enter outpatient addiction treatment initially, then step up to inpatient detoxification if medically necessary, then back down to outpatient or intense outpatient settings. Importantly, this notion of patient movement through levels of treatment has become central to the process of treatment planning for the patient and requires that the clinician plan for the patient's future needs given their current clinical status. As will be discussed, this continuum or levels of care is reflected in the Patient Placement Criteria of the American Society of Addiction Medicine (ASAM).

Clinical matching of patients to therapeutic services: For nearly 40 years, it has been recognized that patients with addictive disorders, despite similarities in diagnoses, have their own complex pattern of psychiatric, psychological, medical, legal, social, and family problems that can impact upon their success in treatment. Thus, not all patients will respond to the specifics of a single unitary type of treatment program within the continuum of care. Consequently, there has been substantial effort directed toward the matching of the patient's clinical presentation to treatment program content or program position within the continuum of care [3].

By determining the specific treatment needs of a patient that are addressed by a given therapeutic program, and then assigning a patient with those needs to that program, it is hoped that there will be an improvement in the overall level of treatment success. Importantly, this strategy emphasizes the conduct of a *systematic multidimensional clinical assessment* to be used for initial treatment placement recommendations, or for determination of continuing care needs. Matching domains include risks to the patient, severity of illness, emotional and cognitive level of functioning, capacity to successfully engage in treatment, relapse potential, and the nature of the recovery environment. Structured and focused clinical assessments such as the Level of Care Utilization System (LOCUS) [4] and the Addiction Severity Index (ASI) [5] have successfully been used for this purpose, and the multidimensional clinical evaluation system offered by the ASAM Patient Placement Criteria [6] (discussed later) is now widely employed and accepted in the determination of patient placement along the continuum of care. Thus, much of our current system of addiction treatment services relies upon the quality of the initial multidimensional clinical assessment, and the serial clinical assessments during the treatment process.

Patient engagement and retention: One of the most critical tasks for an effective drug and alcohol treatment program, clinic or office-based practice, is to encourage patients with substance use disorders to enter and remain in treatment. Unfortunately, evidence has shown that many patients either fail to attend their first treatment session or drop out of treatment after attending only a few sessions. To improve entry and retention, efforts have been directed toward an examination of the process by which patients are referred to treatment, attend their first session, and continue in accordance with the treatment plan. In recognition of this need, SAMHSA's Center for Substance Abuse Treatment (CSAT), and a partnership with the Addiction Technology Transfer Center Network (ATTC Network), and the Robert Wood Johnson Foundation and academic partners have developed the Network for Improvement in Addiction Treatment or NIATx program. This program to teaches drug and alcohol treatment centers and providers how to use process improvement strategies to improve access to and retention in addiction treatment [7]. The specific aims of this program are reducing waiting times between first request for service and first treatment session, reducing the number of patients who do not keep an appointment, increasing admissions to treatment, and increasing continuation in treatment with a focus of the first through the fourth treatment session. Preliminary evaluations of this program have been quite positive [8], yet there remain many addiction professionals who are unaware of its existence or its utility.

Health insurance, managed care, parity, and federal and state financing for addiction treatment services: The concept of *health insurance* in the United States began over concerns for payment during the economic downturn of the Great Depression of the 1930s. Thirty-five years later, *Medicare* was introduced as government-sponsored health insurance to provide coverage to older and retired Americans. By the 1980s, spiraling healthcare costs prompted the emergence of what we now think of as *managed care,* which was an effort to employ greater fiscal responsibility in the allocation and payment for healthcare resources. Managed care introduced price competition by encouraging insurance companies to selectively contract for services such as addiction treatment and mental health services, and award contracts to the most economical providers. By the 2000s, efforts began to control costs by encouraging insured individuals to pay more out-of-pocket using high-deductible health plans. This shift in responsibility for the payment of healthcare services to the patient, disproportionately affected individuals from lower socioeconomic strata and those with limited health insurance benefits, ultimately prompting the passage of the *Patient Protection and Affordable Care Act* (ACA) in 2010.

The early 2000s also showed an organization shift to *integrated healthcare delivery systems* from hospital-based "vertical" systems of care. In an integrated healthcare delivery system, a single organization, or a closely aligned group of organizations, offers a broad range of patient care and support services in a unified manner. However, many of the early integrated healthcare systems avoided incorporating addiction or mental health treatment in their menu of services. The primary argument against providing addiction and mental health treatment was the fear that the cost to third-party payers would be too high, and the outcomes too variable. Many doubted the practicality of requiring insurance providers to cover the costs of parity of substance abuse and mental health treatment services with medical and surgical treatment despite the scientific evidence supporting the benefits of doing so. Key studies conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA) and the RAND Corporation showed that the costs of parity for addiction and mental health treatment are relatively small and that the demonstrable benefits to individuals, employers, and society are highly significant. Consequently, Congress enacted the *Mental Health Parity and Addiction Equity Act* (MHPAEA) of 2008 which now requires health insurers and group health plans to provide the same level of benefits for mental health and/or substance use treatment and services as they do for medical/surgical care. The Affordable Care Act (ACA) further expands the MHPAEA's requirements by ensuring that qualified plans offered cover many behavioral health treatments and services. Specifically, it creates an "essential health benefit" or mandated benefit for the coverage of mental health and substance abuse disorder services in several specific insurance financing arrangements.

States also have an important role in the financing of addiction treatment. *Medicaid* is a Federal/State partnership with shared authority and financing. It is a health insurance program for low-income individuals and people with disabilities. Participation is optional, although all 50 states participate in the Medicaid program to some extent. However, eligibility for specific Medicaid benefits such as those for

addiction and/or mental health treatment varies widely among the states. Currently, the Centers for Medicare and Medicaid Services (CMS) supports a voluntary expansion of *Medicaid* addiction treatment services through a mechanism called Section 1115 demonstration projects that allows states to test innovative policy and treatment delivery for substance use disorders.

Treatment Settings and Levels of Care for Those with Addictive Disorders

The addiction psychiatrist practices in a variety of treatment settings ranging from dedicated addiction treatment programs to general psychiatric and medical/psychiatric specialty venues. The current standardized definitions of the levels of care for addiction treatment cross-cut specialized addiction, psychiatric, medical, and specialty clinical settings. For the practitioner, these defined treatment settings have significant clinical ramifications in terms of appropriateness and availability of treatment type given the patient's clinical needs, established criteria for entry into a given type of treatment, the intensity and duration of treatment, and the financing and reimbursement for the treatments provided. For the program administrator in the managed care environment, these defined treatment settings provide a framework of programmatic standards to assess needs, offer a mechanism to establish and maintain program content, provide a context for program policies and procedures, and compare service coverage with other providers in other venues.

Standardized levels of care in addiction treatment: The current conceptualization of levels of care for addiction treatment was developed and is best exemplified by the American Society for Addiction Medicine (ASAM) Patient Placement Criteria [9]. The ASAM Criteria provide an integrated crosswalk of dimensions of patient characteristics with appropriate levels of care and intensity along the continuum of care, matching patient clinical needs and characteristics with the appropriate treatment services to manage those needs and behaviors. A more detailed explanation of the matching of patient characteristic to a given level of care is available from ASAM [9]. The ASAM criteria have been examined rigorously in terms of their predictive validity for resource utilization and patient outcomes (e.g., [10]). As a result, commercial health insurers recognized the utility of this system of levels of addiction treatment and criteria for entry into a given level of care and began adopting these criteria for both resource management and patient placement.

The passage of the ACA's Medicaid Expansion stimulated the creation of the Medicaid Innovation Accelerator Program (IAP) as a demonstration project to ensure that addiction treatment is delivered consistent with the industry standards. This program employs the ASAM levels of care and treatment criteria because they have become the industry standard and Medicaid is utilizing these criteria in hopes that beneficiaries will receive the most appropriate addiction treatment services given their clinical needs [11]. It is important to note that all localities do not have all these levels of care available to patients, despite encouragement by Medicaid agencies.

The ASAM/Medicaid Adult Levels of Care

Level 0.5: Early Intervention
This level of care incorporates assessment and educational services for those *at risk* of developing an addictive disorder, but who may not meet diagnostic criteria. Included in these early intervention services are screening and brief interventions with referrals to treatment (SBIRT), motivational interviewing, and interventions for driving under the influence (DUI) or while intoxicated, as well as employee assistance programs (EAP).

Level 1: Outpatient Services
The goals of these treatments are to help patients achieve changes in alcohol and/or drug use and addictive behaviors and enhance coping without resorting to substances. This level of care is deemed to be appropriate under four defined conditions:

- An initial level of care for those patients who present with less severe addictive disorders
- An initial level of care for those who are in early stages of change and are not yet prepared for a more intensive treatment experience
- As a "step down" level of care from more intensive services
- A level of care for those who are stable and for whom ongoing monitoring or disease management is appropriate

Medicaid defines Level 1 services as providing *less than 9 hours* of treatment weekly. These services may be delivered in a wide variety of settings ranging from offices, clinics, school-based clinics, and primary care clinics to various facilities that offering treatment or mental health programming.

Level 1: Opioid Treatment Services
Opioid treatment services are programs engaged in the treatment of opioid-dependent individuals with an opioid agonist treatment medication. These services are considered Level 1 programs because services are typically delivered in an outpatient setting. Patients in other levels of care can either be referred to these outpatient programs or treatment can be directly delivered in conjunction with the programming in other levels. Opioid treatment services can provide care in two formats: opioid treatment programs (OTPs) and office-based opioid treatment *(OBOT)* programs.

Opioid treatment programs (OTPs) directly dispense methadone to patients with opioid use disorder without the need to take a prescription to a dispensing pharmacy. These programs are heavily regulated by federal and state agencies.

Office-based opioid treatment (OBOT) is a model of care that permits those physicians who have completed a training course approved by CSAT to obtain a waiver through the Drug Enforcement Administration (DEA) that allows them to prescribe buprenorphine in the outpatient management of individuals with opioid use disorder in office-based settings and in private or public clinics.

Level 2: Intensive Outpatient and Partial Hospitalization Programs
Level 2 programs provide essential psychoeducation and addiction treatment components and are appropriate for patients with co-occurring mental disorders. They can have two levels of therapeutic intensity:

Level 2.1: Intensive Outpatient Programs
Intensive outpatient programs can provide 9–19 hours of weekly structured programming for adults, although Medicaid and commercial insurers typically cap treatment hours at 9. These programs may operate during the day or evening, and on the weekends. Intensive outpatient programs are primarily delivered by addiction outpatient specialty providers but may be delivered in any appropriate setting that meets state licensure or certification requirements. Many of these programs deliver psychiatric, medical, and laboratory services, as well as addiction recovery programming. These programs may have direct affiliation with programs offering more and less intensive levels of care as well as ancillary services such as supportive housing.

Level 2.5: Partial Hospitalization Programs
Partial hospitalization programs are outpatient treatment programs most appropriate for patients with addictive disorders who are living with unstable medical and psychiatric conditions and require daily monitoring and management in a structured setting. Partial hospitalization programs can provide 20 hours or more of clinically intensive programming each week. The setting for this type of addiction treatment program is typically one that is highly structured and offers direct access to psychiatric, medical, and laboratory services. Partial hospitalization programs may be freestanding or located within a larger healthcare system that is distinctly organized from the rest of the available programs.

Level 3: Residential or Inpatient Programs
Residential and inpatient programs provide addiction treatment services in structured settings that are staffed 24 hours/day. These residential levels of care provide a safe, stable environment that is critically important for some individuals as they begin their addiction recovery process. These types of treatment programs may be subdivided into four levels of intensity of services:

Level 3.1: Clinically Managed Low-Intensity Residential Program
Level 3.1 programs are deemed appropriate for patients whose recovery is aided by a time spent living in a stable, structured environment where they can practice coping skills, self-efficacy, and address work, education, and family issues. The goal is to reintegrate the patient to work, school, and family environments. Services are typically provided in a 24-hour environment, such as a group home, and are typically managed by nonphysician addiction specialists rather than medical personnel. Medicaid requires that this level of care provides at least 5 hours of low-intensity treatment services per week that include medication management, recovery skills, relapse prevention, and other similar services. The 5 or more hours of clinical services may be provided onsite or in collaboration with an outpatient service provider.

Level 3.3: Clinically Managed Population-Specific High-Intensity Residential Programs

This level of addiction treatment is specifically designed for a specific population of adult patients with significant cognitive impairments resulting from substance use or other co-occurring disorders including traumatic brain injury. This level of care is appropriate when an individual's temporary or permanent cognitive limitations make it unlikely for them to benefit from other residential levels of care that offer cognitive-based treatment and relapse prevention strategies. These cognitive impairments may be seen in individuals who suffer from an organic brain syndrome due to substance use or age, have developmental disabilities, or suffer from a traumatic brain injury. In general, the pace of therapy is slower, there is more repetition, and the programs are designed to meet the functional limitations of patients. Physicians, physician extenders, and appropriate credentialed mental health and addiction professionals lead the treatments, and there are on-site 24-hour allied health professionals that supervise the residential component.

Level 3.5: Clinically Managed Residential Programs

This intensity of residential addiction treatment is appropriate for individuals whose addiction is so severe and out of control that they cannot be safely treated outside of a 24-hour stable living environment that promotes recovery skill development and deters relapse. Patients receiving this level of care may have severe social and psychological conditions including personality disorders and other psychiatric comorbidities, as well as criminal justice histories and antisocial value systems. However, these co-occurring conditions must be stable enough for the patient to benefit from these programs. Patients typically have minimal risk for a withdrawal syndrome. These programs are often housed in freestanding, licensed facilities located in a community setting or a specialty unit within a licensed healthcare facility. Treatment is typically provided by an interdisciplinary team made up of appropriately credentialed clinical staff including addiction counselors, social workers, and licensed professional counselors, and allied health professionals who provide residential oversight. Telephone or in-person consultation with a physician is a required support, but on-site physicians are not required by Medicaid.

Level 3.7: Medically Monitored Inpatient Programs

This level of care is appropriate for patients with biomedical, emotional, behavioral, and/or cognitive conditions that require highly structured 24-hour services including direct evaluation, observation, and medically monitored addiction treatment, but do not meet severity requirements for an acute care hospitalization or a medically managed inpatient addiction treatment program. Individuals at heightened risk for a withdrawal syndrome, but who do not require a hospital environment, are appropriate for Level 3.7 facilities. For those with psychiatric comorbidities, a specialized treatment track is usually a component of the services. Treatment is provided by an interdisciplinary team which is made up of physicians credentialed in addiction who are available on-site 24 hours daily, registered nurses, and additional appropriately credentialed nurses, addiction counselors, and ancillary staff who are knowledgeable

about biological and psychosocial dimensions of addictive and psychiatric conditions. These programs are typically housed in freestanding, appropriately licensed facilities located in a community setting or a specialty unit in a general or psychiatric hospital or other licensed healthcare facility.

Level 4: Medically Managed Intensive Inpatient Programs
This level of care is appropriate for patients with biomedical, emotional, behavioral, and/or cognitive conditions which are severe enough to warrant primary medical and nursing care. Examples include addicted patients with seizures, endocarditis, sepsis, pregnancy complications, or liver failure. This level is also appropriate for unstable patients who have comorbid mental and addictive disorders whose management is complicated by their medical problems. Addiction services including medically directed acute withdrawal management are provided in conjunction with intensive medical and psychiatric services. It is noteworthy that services offered at Level 4 differ from Level 3.7 services in that patients receive daily direct care from a licensed physician who is responsible for making shared treatment decisions with the patient. These services are typically provided in a hospital-based setting and include medically directed evaluations and treatments, and 24-hour/day nursing care. The treatment venues for this level of care include acute-care hospitals, psychiatric hospitals, or psychiatric units in general hospitals, and those specialty addiction treatment hospitals that have a strong medical management component.

Levels of Care for Adolescent Treatment

It is well-recognized that the manifestations of addictive disorders and the treatment needs of adolescents may not be congruent with those for adults. The biopsychosocial environment for adolescents is very different from that of adults, and the factors that bring adolescents into treatment and their responses to treatment are frequently quite different from adults. In recognition of these differences, the most recent version of the ASAM criteria [9], and the ASAM/Medicaid criteria, has incorporated specific matching criteria for the level of care, the appropriateness of treatment venues (e.g., school-based clinics, after-school and weekend treatment programming), and the intensity of treatments based upon the best evidence of the needs of the adolescent patient.

Quality Performance Measures and Health Services for Addictive Disorders

Providers, patients, and payers are increasingly emphasizing the measurement of value and performance in the delivery of health services. Consequently, the treatment of addictive disorders is the focus of quality and performance scrutiny, and the development of suitable measures of quality performance is underway. The most

advanced of these measures are derived from ASAM's Standards of Care for the Addiction Specialist Physician [12]. Currently, nine specific performance measures have been developed by ASAM for the treatment of alcohol use disorders and opiate use disorders [13]. These measures are:

- *MEASURE #1*: Percent of patients prescribed a medication for alcohol use disorder (AUD)
- *MEASURE #2*: Percent of patients prescribed a medication for opioid use disorder (OUD)
- *MEASURE #3*: Number of patients receiving 7-day follow-up visit after withdrawal management
- *MEASURE #4*: Presence of screening for psychiatric disorder
- *MEASURE #5:* Presence of screening for tobacco use disorder
- *MEASURE #6:* Number of patients receiving primary care visit follow-ups within 6 months of treatment initiation
- *MEASURE #7:* All cause inpatient, residential re-admission following initial treatment episode
- *MEASURE #8*: The presence of SUD diagnosis documentation in addiction treatment regardless of setting
- *MEASURE #9*: Number of psychiatric disorder diagnoses present

Currently, Medicaid and several commercial health insurers are testing the utility of these ASAM quality performance measures to determine their acceptability, feasibility, and informativeness. While these and other quality performance indicators are not yet a part of our current practice requirements, such measures are soon likely to have an important role in the practice of addiction psychiatry.

Review Questions

JB is a 39-year-old male businessman with a history of heavy drinking that began in high school when his girlfriend broke up with him. After a recent divorce, his drinking increased to daily binge drinking that he seems to have no control over. Laboratory tests from a recent annual physical exam revealed marked elevations in both AST and ALT which prompted his primary care doctor to screen for an alcohol use disorder using the MAST (Michigan Alcoholism Screening Test). JB screened positive, and his physician discussed his drinking behavior with him and recommended that he cut down on his use of alcohol. When JB attempted to do so, he became severely anxious, tremulous, and sweaty. He went to the local emergency department, but he was so uncomfortable and shaky in the waiting room that he decided to go home. His only relief came after he impulsively consumed three shots of his usual alcoholic beverage. He called his primary care physician back and explained what had transpired. He was skeptical that anything could help him but accepted a referral to a local substance use treatment program for an intake evaluation.

1. What is the purpose of the intake evaluation?
   A. To reduce the primary care physician's clinical burden
   B. To evaluate whether JB could pay for treatment out-of-pocket
   C. To determine the appropriate level of care for JB's initial treatment
   D. To ensure that JB had no legal issues pending
   E. To introduce JB to the program staff

   Best Answer: C. To determine the appropriate level of care for JB's initial treatment

   Explanation: A multidimensional assessment is fundamental to determining the level of care that best matches the patient's clinical presentation.

2. Which of the following was most influential in determining JB's initial level of care?
   A. His history of failed relationships
   B. His history of alcohol withdrawal symptoms
   C. His elevated liver enzymes
   D. His preferred alcoholic beverage
   E. His skepticism about treatment helping him

   Best Answer: B. His history of alcohol withdrawal symptoms

   Explanation: According the ASAM/Medicaid criteria, risk for a withdrawal syndrome is a criterion to determine the need for heightened medical monitoring or inpatient status for a patient.

   JB was admitted to a medically monitored residential treatment program. He experienced moderate alcohol withdrawal symptoms which were managed by the physician and treatment team over the next 5 days. After a week in the program, JB begins to talk in groups and engage in therapy. However, his mood remained low despite his abstinence from alcohol. The program physician began a trial of antidepressant medications. The treatment team continued to assess JB for other relevant clinical issues. In parallel with this clinical assessment, the treatment team began discharge planning. They recommended that upon discharge, JB continue treatment in an Intensive Outpatient Program that is a component of this community addiction treatment program.

3. ASAM Standards of good clinical practice in addiction treatment suggest that patients should be evaluated for which if of the following?
   A. Work and financial status
   B. Transportation and housing needs
   C. Tobacco use disorders
   D. Need for marital or couple's therapy
   E. Pharmacogenetic metabolic status

   Best Answer C. Tobacco use disorders

   Explanation: According to the ASAM's Standards of Care for the Addiction Specialist Physician screening for tobacco use disorders is one of the quality performance measures for the addiction professional.

4. What does JB's transition from a residential treatment program to an Intensive Outpatient Program reflect?
   A. His poor response to initial treatment
   B. Concerns that he cannot afford the residential program
   C. His potential to have a conflict with other patients
   D. The availability of a continuum of care
   E. His unresolved depressive symptoms

Best Answer: D. The availability of a continuum of care

Explanation: In addiction treatment the "continuum of care" is interpreted as a fluid treatment system in which patients initially enter treatment at a level appropriate to their clinical needs, and then step up to more intensive treatment or down to less intense treatment as clinically indicated. JB's transition to an Intensive Outpatient Program is a less intensive treatment.

References

1. Dennis M, Scott CK. Managing addiction as a chronic condition. Addict Sci Clin Pract. 2007;4(1):45–55.
2. McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. JAMA. 2000;284(13):1689–95.
3. McLellan AT, Woody GE, Luborsky L, O'Brien CP, Druley KA. Increased effectiveness of substance abuse treatment. A prospective study of patient-treatment "matching". J Nerv Ment Dis. 1983;171(10):597–605.
4. Sowers W, Pumariega A, Huffine C, Fallon T. Level-of-care decision making in behavioral health services: the LOCUS and the CALOCUS. Psychiatr Serv. 2003;54(11):1461–3.
5. McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, et al. The fifth edition of the addiction severity index. J Subst Abus Treat. 1992;9(3):199–213.
6. Gastfriend DR, Mee-Lee D. The ASAM patient placement criteria: context, concepts and continuing development. J Addict Dis. 2003;22(Suppl 1):1–8.
7. Hoffman KA, Green CA, Ford JH II, Wisdom JP, Gustafson DH, McCarty D. Improving quality of care in substance abuse treatment using five key process improvement principles. J Behav Health Serv Res. 2012;39(3):234–44.
8. Rutkowski BA, Gallon S, Rawson RA, Freese TE, Bruehl A, Crèvecoeur-MacPhail D, et al. Improving client engagement and retention in treatment: the Los Angeles County experience. J Subst Abus Treat. 2010;39(1):78–86.
9. Mee-Lee D, Shulman GD, Fishman MJ, Gasfriend DR, Miller MM, editors. The ASAM criteria: treatment criteria for addictive, substance-related and co-occurring conditions. 3rd ed. Carson City: The Change Companies; 2013.
10. Sharon E, Krebs C, Turner W, Desai N, Binus G, Penk W, et al. Predictive validity of the ASAM patient placement criteria for hospital utilization. J Addict Dis. 2003;22(Suppl 1):79–93.
11. C.M.S. Overview of substance use disorder (SUD) care clinical guidelines: a resource for states developing SUD delivery system reforms [PDF]. Washington, DC: U.S. Department of Health and Human Services; 2017. [updated 04/2017; cited 2018]. Available from: https://www.medicaid.gov/state-resource-center/innovation-accelerator-program/iap-downloads/reducing-substance-use-disorders/asam-resource-guide.pdf.
12. (ASAM) ASoAM. Standards of care for the addiction specialist physician. 2014. Available from: https://www.asam.org/docs/default-source/publications/standards-of-care-final-design-document.pdf.
13. (ASAM) ASoAM. The ASAM performance measures for the addiction medicine physician. 2014. Available from: https://www.asam.org/docs/default-source/advocacy/performance-measures-for-the-addiction-specialist-physician.pdf?sfvrsn=5f986dc2_0.

Laboratory Testing for Substance Use Disorders

2

David Dadiomov

High-Yield Review Points

- Drug screening interpretation can be highly affected by patient-specific factors such as time since last use, metabolism, genetics, age, and weight.
- Knowledge of drug-specific factors such as half-life, tissue binding, and metabolism can help the clinician properly interpret a drug screening result.
- A thorough and accurate patient history is necessary prior to drug screening to interpret possible false-positives or negatives.
- Certain medications require baseline medical laboratory testing which should be conducted and followed to ensure safe use.

Introduction

Laboratory drug testing is an important tool utilized by clinicians for the comprehensive assessment of patients with substance use disorders. Drug screening gives a clinician objective evidence regarding the presence of various substances or metabolites with which inferences can be made about consumption of substances. Drug screens may be commonly utilized in nonmedical settings (such as for employment or legal purposes); however, it is important to discern these tests from those utilized in clinical practice. In the employment setting, false positives may carry severe implications, and thus detection limits for these are often higher. However, in the clinical setting, many factors may impact the result of a drug screen, and thus a greater level of detail is warranted in ordering and interpretation of laboratory results.

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Due in part to the societal stigma associated with drug screening, patients may have concerns that should be addressed. The reason for laboratory testing should be communicated, and both the patient and provider should have an agreement or understanding about how and why drug screens are conducted. In general, testing should be conducted in accordance with the patient's pattern of use, their stage in the recovery process, the substances used, and any practical considerations (such as transportation and schedule). This chapter will discuss the fundamentals of testing across different clinical scenarios.

Prior to interpreting urine drug screens, it is imperative that the clinician perform a thorough history of all products a patient has used and the time of last use. This medication history should include all licit, illicit, over-the-counter, and herbal products the patient may be using. Proper interviewing techniques (such as utilizing open-ended questions) should be employed to elicit a thorough history. Many substances have the potential to be detected as a false positive; these instances can be excluded if known. In addition, substances can vary significantly in their pharmacokinetic properties, and the timing of last use can help a clinician properly interpret results.

Principles of Laboratory Testing

Laboratory screening in SUD can be conducted for two major purposes, either to assess the safety of a given medication and conduct general medical testing or to assess the presence of substances or their metabolites. When conducting general medical testing, typically clinicians may be obtaining baseline labs to ensure a patient doesn't have a contraindication to a particular therapy (e.g., renal or hepatic impairment), as well as monitoring for laboratory abnormalities potentially caused by the medication. In contrast, when conducting drug screening the primary goal may be to assess that the patient is adherent to their prescribed regimen. It may also serve to assess whether a patient is diverting the medication or utilizing other substances. This chapter will focus primarily on drug screening; however, other elements of laboratory testing will be discussed when relevant.

A variety of drug screening tools are currently available to clinicians. Likely the most familiar of these tests will be immunoassay tests. These are usually "dipstick" urine tests that can be used for initial screening; however, they have lower sensitivity and specificity than confirmatory or laboratory tests via gas chromatography/mass spectroscopy (GCMS). Immunoassays are limited by their qualitative nature and higher proportion of false positive and false negative test results as compared to the quantitative tests. Urine immunoassays typically have a threshold, above which a specimen is considered to be positive. Typically, an immunoassay is used as a preliminary tool. If the test returns positive, it is usually sent for further confirmatory testing [1]. Despite several disadvantages, urine immunoassays are typically quick and easy to conduct and are inexpensive. Often immunoassays may be employed as a cost-savings tool when a high level of precision is not needed.

Table 2.1 Federal urine drug screening cutoffs [1–3]

Substance	Initial cutoff value	Typical urine detection window
Marijuana (THC)	50 ng/mL	Single use – 2–3 days Moderate use – 5–7 days Chronic use – >30 days
Cocaine (benzoylecgonine)	150 ng/mL	3 days
Codeine/morphine	2000 ng/mL	2 days
Hydrocodone/hydromorphone	300 ng/mL	3 days
Oxycodone/oxymorphone	100 ng/mL	3 days
6-Acetylmorphine	10 ng/mL	2 days
Phencyclidine	25 ng/mL	7 days
Amphetamine/methamphetamine	500 ng/mL	2 days
MDMA/MDA	500 ng/mL	2 days

It is important for clinicians in addiction psychiatry to be aware of the detection limits of any test they are employing for clinical decision-making. The average detection limit for urine immunoassays tends to be relatively high to minimize the occurrence of false positives. Federal guidelines set guidelines for workplace urine drug screening cutoff levels (Table 2.1) [2]. In addition, the Department of Health and Human Services (HHS) has established a standard guideline for workplace drug screening, typically known as the "standard 5 panel drug test." This panel includes screening for marijuana, cocaine, phencyclidine (PCP), amphetamines, and certain opioids. As discussed further in this chapter, there are limitations to specific substances that can be detected on the standard drug screen.

Within addiction psychiatry, however, obtaining quantitative tests may be of greater clinical utility. With standard immunoassays, a patient's sample may be falsely negative for a variety of reasons including genotypic metabolism differences, a subthreshold positive result, or the particular substance or metabolite is not detected [1]. Furthermore, urine immunoassays may have many false positives and false negatives that limit their utility in addiction settings. A false-positive test may be the result of a substance used that has a similar chemical structure to the assayed chemical and thus shows up as a positive result. Agents that can cross-react for a false-positive test can be medications, herbal supplements, and food products.

Clinicians also have a variety of sampling methods for drug screenings (Table 2.2). Most commonly utilized are urine, blood, hair, nail, and breath tests. Urine tests are the most commonly employed due to their relative ease of collection, and good detection window for most substances or their metabolites. Blood sampling may be more useful for detecting acute intoxication as it has a shorter detection window. Conducting hair and nail testing leads to the longest detection window; however, there is also a delay for the substance to appear in the sample after use, and there are specific guidelines about how to collect hair and nail samples. Breath testing is also typically used primarily to detect acute intoxication of volatile substances such as ethanol and is very easy to administer in most environments [4].

In addition to ordering the best test for the setting and need, it is imperative that an addiction psychiatrist can interpret tests correctly. As mentioned previously,

Table 2.2 Benefits and drawbacks of different drug screening methods

Sampling method	Benefits	Drawbacks
Urine	Relatively inexpensive, readily available, quick results, noninvasive sample collection	Limited accuracy for certain compounds, adulteration risk if unsupervised
Blood	May determine acute intoxication, relatively inexpensive	Invasive, will not determine past drug use
Hair	Long period (3–6 months) of detecting past use, noninvasive sample collection	Will not detect recent drug use, expensive
Nail	Long period of drug detection to hair test, noninvasive collection	Will not detect recent drug use, expensive
Breath	Readily available, inexpensive, determines acute intoxication	Primarily only for volatile drugs (ethanol)

Table 2.3 Potential positive results for substances of misuse [1]

Substance	Potential positive result
Amphetamines	Aripiprazole, atomoxetine, bupropion, ephedrine, labetalol, MDMA, phentermine, pseudoephedrine, ranitidine, selegiline, trazodone, Vicks inhaler
Benzodiazepines	Efavirenz, sertraline
THC	Dronabinol, efavirenz, nabilone
Opioids	Dextromethorphan, diphenhydramine, poppy seeds, quinolone antibiotics
Phencyclidine	Dextromethorphan, doxylamine, ketamine, tramadol, venlafaxine

knowledge of full medication history is important as many substances may cause false positives in immunoassays. The clinician should consider the false-positive and false-negative rate of many available immunoassays (Table 2.3), though this can vary by manufacturer for each test. Knowledge of physical properties of various substances is important to being able to predict the results of a given drug screen. For instance, the metabolic pathway of a given substance may produce analytes that could incorrectly be interpreted as the use of a different substance if the interpreter doesn't recognize the full pathway. Information on specific substances will be discussed in this chapter. Other pharmacokinetic considerations should be noted, such as the half-life and tissue binding of a substance and/or its metabolites which would dictate the time frame that a test may be valid. Finally, individual pharmacogenomics may alter the analytes in a specimen as well. This may occur when individuals are poor or ultrarapid metabolizers of a substance.

Providers should also consider ways of manipulation of the sample if there is an incentive to do so. While some samples are less likely to demonstrate interference (such as blood or breath tests), unobserved urine samples may lend themselves to adulteration. In these instances, a urinalysis is recommended to provide information for interpretation. The sample would be expected to have a temperature close to normal body temperature. The color of the sample, urine creatinine, specific gravity, and pH should be within normal homeostatic ranges (Table 2.4) [5].

Table 2.4 Homeostatic urinalysis ranges

Criteria	Range
Urine creatinine	18–200 mg/dL
pH	4.5–8.0
Specific gravity	1.002–1.030
Temperature	90–100 °F

Drug-Specific Information

Opioids

Opioids broadly describe the substances that have agonist activity at the mu opioid receptors, as well as other opioid receptors. Naturally occurring opioids can be further classified as opiates, whereas semisynthetic and fully synthetic opioids require some manipulation for their manufacture and are chemically distinct. Opioids contain differing pharmacokinetic properties which can vary depending on their specific formulation (e.g., extended release tablets). These different properties carry implications for detection in drug screens. For instance, opioids that are formulated in a long-acting or extended release formulation may be detectable in specimens for a longer period. Additionally, most urine drug screens are not as sensitive for semisynthetic opioids such as oxycodone and hydrocodone nor synthetic opioids such as fentanyl. In instances where the clinician wishes to test for those opioids, a specific test will need to be ordered.

Another important consideration for those caring for patients with opioid use disorders is the metabolism of the different opioids. Figure 2.1 demonstrates a general pathway for opioid metabolism. Of note, the opioid metabolism pathway of many opioids may converge at several common metabolites. For instance, a patient taking either codeine, morphine, or heroin may produce a urine specimen that contains morphine. Therefore, a patient that is prescribed acetaminophen and codeine tablets, and takes a urine drug screen (UDS) that shows a positive result for morphine, should not necessarily be accused of use of other substances. Similarly, utilizing various analytes and their concentrations may help discern use of one substance from the other. A patient that is abusing heroin (aka diacetyl morphine) would show morphine in their UDS, just as a patient taking morphine or codeine would. However, a test for the analyte 6-monoacetyl morphine is specific to the heroin metabolite and would indicate heroin use. However, 6-monoacetyl morphine has a fairly short detection window in the urine of 8 hours [1].

Providers should be aware that many synthetic opioids (such as fentanyl, methadone, or buprenorphine) do not show up on standard drug panel and will typically require a specific lab test for these agents [1]. If taking care of patients who may be using synthetic opioids, it is important to ensure that the capability to order these specific lab tests exists.

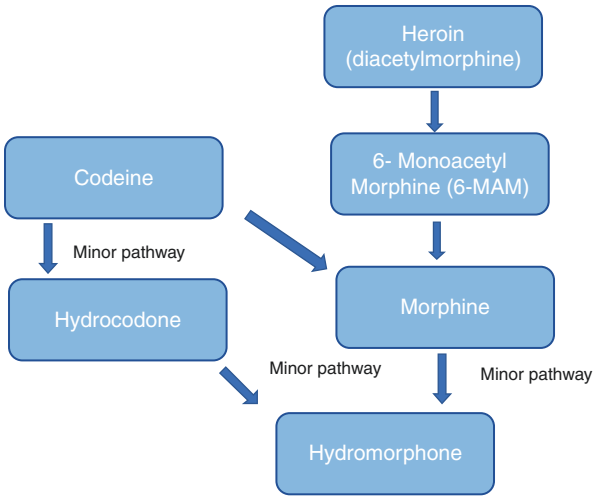


Fig. 2.1 Opioid metabolism [6]

Buprenorphine is a synthetic opioid commonly used in both treatment of pain as well as treatment of opioid use disorder. Clinicians may wish to order buprenorphine urine testing for several reasons. Since it is a mu-opioid partial agonist, there is a potential for buprenorphine misuse. Patients may be acquiring illicit buprenorphine and the provider wishes to assess the use pattern. Another reason for buprenorphine drug screening is to ensure adherence to the regimen for opioid use disorder. This serves as a marker of medication ingestion and to minimize diversion of buprenorphine. Urine testing of buprenorphine/naloxone products should include buprenorphine and norbuprenorphine (major metabolite) [7]. Providers should carefully consider the pattern of detection that would be expected with adherence as compared to adulterated samples. A patient taking buprenorphine/naloxone formulation would be expected to produce a sample containing buprenorphine and norbuprenorphine. Additionally, some laboratories may report naloxone concentrations; a proportion of the naloxone may be absorbed sublingually and thus be detectable in the urine. Some laboratories may report naloxone concentrations as either free naloxone, naloxone-3-glucuronide, or total naloxone concentrations [8, 9]. Analysis of free naloxone in urine may indicate adulteration, whereas naloxone-3-glucuronide is the expected analyte from first pass metabolism of oral or sublingual naloxone.

Methadone is another synthetic opioid that is commonly used for both treatment of pain as well as opioid use disorder. Again, special laboratory testing is required to detect methadone in the urine. Methadone testing is prone to adulteration of urine with drug. To determine if methadone was added to urine (as opposed to being present via excretion of the drug into urine), clinicians may choose to order a test for methadone's metabolite 2-ehtylidene-1,5-dimethyl-3,3-diphenylpyrollidine (EDDP). The presence of EDDP would indicate that the patient has ingested and metabolized methadone [1].

Alcohol

Alcohol is one of the most commonly used substances and may often co-occur with other substance use or mental health disorders. Alcohol has slightly different pharmacokinetics from many other substances. In general, ethanol undergoes metabolism that is termed "zero-order" kinetics, or saturable pharmacokinetics. This implies that the metabolism of alcohol occurs at a given metabolic rate (20 mg/dL/hour) regardless of the concentration of alcohol in the body; thus, the metabolism is "saturable." Several factors may affect this metabolic rate such as sex (women eliminate alcohol faster, though they have higher blood alcohol concentrations because of a smaller volume of distribution), race, whether someone is in the fed nutritional state, and body mass [10].

The usual laboratory measurement for alcohol in clinical settings is the blood alcohol content (BAC) expressed as mg of ethanol per dL of blood. BAC may be recognized as its expression of a percentage, as in the legal limit to operate a motor vehicle that is 0.08%. A BAC of 0.1% corresponds to 100 mg ethanol/dL blood. A "standard drink" in the United States is defined as 14 g of ethanol, or 0.6 fluid ounces of pure ethanol. Similarly, this corresponds to a 12 oz beer (5% ABV), a 5 oz glass of wine (12% ABV), or 1.5 oz of spirit (40% ABV).

BAC is easily estimated using a breathalyzer machine which can give clinicians a quick reading of estimated BAC. Due to the ease and affordability of testing, the comorbid presence of alcohol use disorders with other substance use disorders, and the negative implications of alcohol intoxication to recovery, many clinicians will utilize a breathalyzer in routine outpatient follow-up. In addition, patients newly presented to inpatient units or emergency departments may obtain a blood draw to determine their alcohol content to guide further treatment considerations.

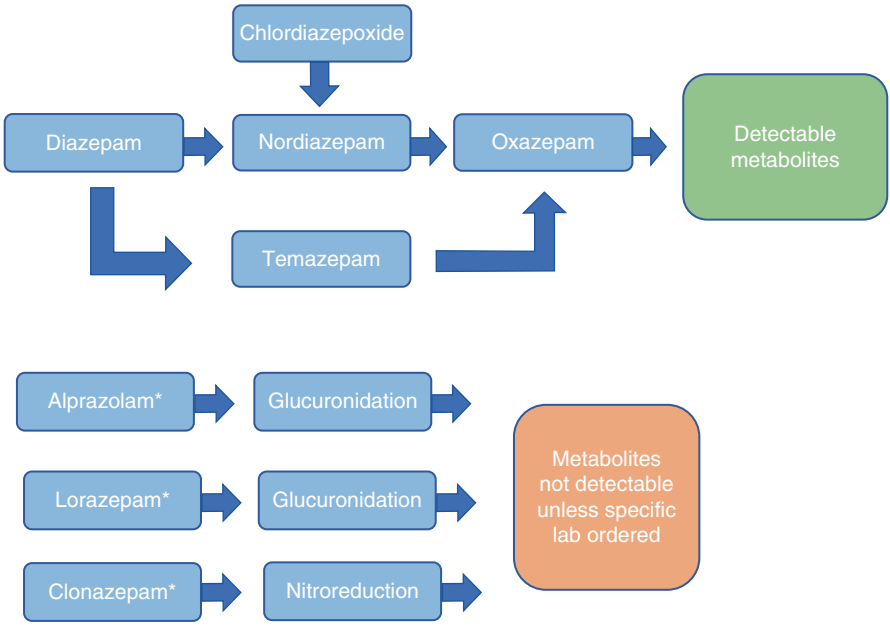
In addition to labs to detect acute intoxication, several other forms of laboratory testing may be utilized to assess patients with alcohol use disorders. While ethanol has a fairly short half-life, it is metabolized to ethyl glucuronide and ethyl sulfate which are excreted in the urine. Ethyl glucuronide may be detected for up to 3–4 days after alcohol consumption. Ethyl sulfate may be used concurrently to increase the specificity of the ethyl glucuronide test [11]. Another test for ethanol consumption utilized is phosphatidyl ethanol. Phosphatidyl ethanol is elevated in the presence of 4–5 standard drinks per day for at least 3 weeks. It remains elevated for up to 14 days from discontinuing alcohol [11]. Gamma glutamyl transferase (GGT) is a liver enzyme that is increased in individuals with chronic heavy alcohol use. In patients without chronic heavy alcohol use, GGT levels are expected to be below 54 IU/L. It should be noted that certain anticonvulsant medications may increase a patients GGT even without alcohol use. GGT may also be increased in certain hepatic conditions, and so it is not specific for alcohol use. Carbohydrate-deficient transferrin (CDT) is a protein that exists in blood and is increased with heavy alcohol use. Elevations in carbohydrate-deficient transferrin may be noted sooner than elevations in GGT. A value greater than 1.6% indicates heavy alcohol consumption. Finally, standard liver function panel labs may be assessed in alcohol use disorder. Liver function tests (LFTs) such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and mean corpuscular volume (MCV) may be increased with repeated alcohol use. Elevations in LFTs have been associated with

hepatic cellular damage due to toxins, and MCV elevations are more likely a result of direct hematologic toxicity of ethanol, rather than vitamin deficiencies. These tests are not as sensitive or specific as those previously listed [11].

Benzodiazepines

Benzodiazepines are also commonly used agents for anxiety and related disorders that have also been widely misused. As with other substances, it is important to consider the pharmacokinetics of the specific agent that is being detected. Benzodiazepines vary in their half-lives with some having a half-life as short as 10 hours (alprazolam), and others lasting 3 days or longer (diazepam). Diazepam has a half-life of 72 hours; however, its active metabolite desmethyldiazepam has a half-life of 160 hours. Due to the drug lingering in the body for so long, diazepam may be detected for up to 30 days [1].

Urine immunoassays for benzodiazepines unfortunately have a high rate of false negatives. Most assays are designed to detect diazepam or its metabolites such as nordiazepam, or oxazepam. Benzodiazepine metabolites as a result of glucuronidation in liver metabolism (such as metabolites of alprazolam or lorazepam) are often not detected on standard immunoassays. Similarly, clonazepam is metabolized by nitroreducation, and its metabolite is not often detected (Fig. 2.2). A small proportion



*A small minority of these benzodiazepines are excreted unchanged in the urine. Even without specific lab testing, they may be detected but usually with less sensitivity and at high concentrations.

Fig. 2.2 Benzodiazepine metabolites

of these benzodiazepines (alprazolam, lorazepam, and clonazepam) are excreted in the urine unchanged and may therefore be detected by urine drug screens. Careful consideration is warranted for the assays cutoff value for detection. Potent agents requiring lower doses (such as alprazolam or lorazepam) may not show up on an assay if the cutoff for detection is 300 ng/mL. Agents that undergo metabolism that is not readily detectable on immunoassay further decrease the likelihood of detection as only a small proportion of the original dose is available to be detected.

Tests that are specific for these compounds can be helpful in detecting an individual's use of benzodiazepines. In some instances, lower detection cutoffs may be available and useful for detecting potent or glucuronidated benzodiazepines. Finally, some laboratories are able to enzymatically alter the benzodiazepine metabolites to the parent drug via hydrolysis of the urine sample [1].

Marijuana

Urine drug screens focus on detecting a metabolite of the main psychoactive component of marijuana, delta-9 tetrahydrocannabinol (THC). Typically, the federal cutoff limit for detection is 50 ng/mL [2]. Several factors may affect how long THC may be detectable in an individual. The first consideration should be whether the user is a chronic smoker or not. In infrequent users, THC may be detectable for only 3 days. However, chronic heavy users may be detectable for 30 days or longer due to elution of THC that was stored in body tissues. A positive immunoassay will not be able to distinguish acute intoxication from use that may have occurred several days ago.

A commonly held misconception about marijuana is that passive inhalation (such as from a concert) may produce a positive result. This has been tested in a controlled environment, and while nonsmokers in an enclosed environment had some THC metabolites detectable on GCMS (mean ranging from 7.5 to 28.3 ng/mL depending on THC concentration in marijuana and whether ventilation was in the room). The results demonstrated that only 1 of the 6 subjects had a positive result above the federal threshold of 50 ng/mL with high-potency marijuana in an enclosed environment with no ventilation. The result was only positive at 4–6 hours post exposure, and subsequent specimens fell below 50 ng/mL. Therefore, it is highly unlikely to test positive for passive inhalation in an instance where exposure is not obvious [12].

Synthetic Cannabinoids

Synthetic cannabinoids have been developed and widely used due to their similar effects to cannabinoids and their difficulty in detection on standard drug tests. Synthetic cannabinoids represent a diverse array of chemicals that are often sprayed onto inert plant material and smoked in a similar fashion to marijuana [13]. The DEA has banned many of these synthetic compounds because of numerous poison center reports [1]. Despite the fact that standard federal panels do not test for

synthetic cannabinoids, there is increasing development of urine immunoassays to detect these substances. Several validated immunoassays are available, but it is important for clinicians to recognize that not all synthetic cannabinoids have an associated screening tool and further development of novel cannabinoids may occur in the future. The usual detection time reported for synthetic cannabinoids is 72 hours; however, this detection window may be increased in chronic users [1].

Stimulants

Stimulant medications are commonly prescribed for disorders such as ADHD, though they are frequently misused as well. This class includes drugs such as amphetamine, methylphenidate, methamphetamine, and cocaine. UDS for stimulants can be challenging for clinicians due to the poor selectivity of these assays, specifically those screening for amphetamines. Due to chemical similarities, the distinction between amphetamine and methamphetamine is difficult to make without a more quantitative laboratory analysis [1]. Clinicians should be aware that many prescribed and over-the-counter medications may cause false positives (and even some "true" positives) on UDS. For instance, the MAOI selegiline is metabolized to methamphetamine in the body and may trigger a positive UDS. Oxymetazoline (Vicks) nasal spray has also been shown to produce a positive urine screen after following manufacturer-recommended dosing [1]. False positives for amphetamine screens may include aripiprazole, atomoxetine, bupropion, chlorpromazine, ephedrine, metformin, MDMA, phentermine, pseudoephedrine, ranitidine, and trazodone, among others. The standard federal 5 panel drug screen includes confirmatory testing for MDMA (methalenedioxymethamphetamine or "ecstasy") as well as MDA (methylenedioxyamphetamine). If a urine screen is positive for amphetamines, it is recommended to utilize quantitative confirmatory testing (e.g., GCMS testing) to verify the result. Amphetamines or methamphetamines are typically detected in the urine for about 48–72 hours after use [1, 3]. It should be noted that to detect methylphenidate accurately, a specific laboratory test for it should be ordered.

Cocaine, on the other hand, is a urine screen that has a high level of specificity, and no false positives have been identified for this assay [1, 3]. Cocaine assays screen for benzoylecgonine: a metabolite of cocaine. It is detectable in the urine for 2–4 days after use [1]. Cocaine is a schedule II substance by the FDA and is often used licitly as an eye drop in ophthalmic procedures. It is reasonable that use under these circumstances may produce a positive test result; however, other aminoester or aminoamide local anesthetics (such as benzocaine and lidocaine) do not produce false-positive results [1].

Nicotine is the legal stimulant present in tobacco leaves and also sold over-the-counter in gums, patches, and lozenges. It is present in many "vapes" as a heated and inhaled liquid. Many patients who misuse substances are concomitantly dependent on nicotine. When assessed, providers are able to order a urine screen on nicotine's major metabolite, cotinine. Cotinine can be detected in the urine of heavy smokers for up to two weeks [14].

Dissociatives

Dissociative drugs include phencyclidine (PCP), ketamine, and dextromethorphan. These agents produce perceptual disturbances, hallucinations, and characteristic out of body (dissociative) experiences. PCP is included in the standard federal 5 panel drug test. While PCP is a schedule I controlled substance, ketamine and dextromethorphan are commonly used in medical care. These agents have the potential to show up as a false positive for PCP. The use of these agents should be excluded prior to interpreting a positive UDS. PCP is typically detected in the urine for up to a week following its use [3].

Hallucinogens and Other Drugs

Hallucinogens include substances such as psilocybin (active ingredient in psychedelic mushrooms), lysergic acid diethylamide (LSD), and mescaline (found in peyote cactus) have not historically been detected on standard urine drug screens. In many instances, these substances have short half-lives or are sufficiently potent that only a small amount of drug is needed for recreational use. While specialized laboratory testing is available, it is fairly uncommon in clinical practice. Other substances besides hallucinogens that may be difficult to detect on a urine screen include gamma-hydroxybutyrate (GHB), inhalants, and synthetic cathinones ("bath salts") [3].

Review Questions

1. A patient enrolled in your opioid use disorder clinic presents for a routine follow-up and refill for their buprenorphine prescription. The patient submits a urine drug screen prior to the appointment. The clinician reviews the results which indicate a positive result for morphine and 6-monoacetyl morphine. What is the most likely substance this patient was using?
   A. Morphine
   B. Heroin
   C. Codeine
   D. Oxycodone
   E. Hydromorphone

   Correct answer: B. Heroin

   Explanation: Heroin, or diacetyl morphine, is converted in the body to 6-monoacetyl morphine and then to morphine. Morphine use alone would not explain the presence of 6-monoacetyl morphine. Codeine would show up as codeine and morphine. Oxycodone and hydromorphone are semisynthetic opioids that would not be expected to contain morphine nor 6-monoacetyl morphine in their metabolic pathway.

2. A patient presents to the emergency department for aberrant behavior. The clinical staff suspect the patient's behaviors may be due to ingestion of substances. The physician on the team orders a urine drug screen, but would like to consider substances that may not be readily detectable by urine immunoassay. Identify the substance that is least likely to be detected on a standard urine drug screen.
   A. Phencyclidine
   B. Marijuana
   C. Diazepam
   D. Bath salts
   E. Mixed amphetamine salts

   Correct answer: D. Bath salts

   Explanation: Bath salts are not one of the standard items that can be detected on urine drug screens, and would require highly specialized tests to detect. PCP, marijuana, diazepam, and amphetamines are all detected as part of the standard federal 5 panel drug test.
3. A patient is seen for detoxification of alcohol; however, the patient is not able to give a reliable medical or social history. The medical team would like to determine whether the extent to which the patient has been consuming alcohol. Which laboratory test would best identify a patient that has been using alcohol excessively over a prolonged period?
   A. Phosphatidylethanol
   B. Ethyl glucuronide
   C. Alcohol breath test
   D. Albumin
   E. Serum creatinine

   Correct answer: A. Phosphatidylethanol

   Explanation: Phosphatidylethanol, elevated GGT, or carbohydrate-deficient transferrin can be used to identify patients with prolonged alcohol use. Ethyl glucuronide is useful for detecting use within past 3–4 days, and alcohol breath test for patients that have recently ingested alcohol. The albumin and serum creatinine are not used to assess alcohol use.
4. A 31-year-old male presents to the addiction clinic for treatment of opioid use disorder. The patient claims to use opioids regularly and would like to "get clean." He submits a urine sample in the office for a standard immunoassay. The results come back and are negative for opiates, benzodiazepines, PCP, marijuana, and amphetamines. The physician runs the state prescription drug monitoring program and discovers the patient has had multiple pharmacy refills in the past month for fentanyl and alprazolam. Which of the following statements is correct regarding the results of this patient's immunoassay?
   A. The patient is likely not using any substances and is seeking buprenorphine for diversion.
   B. The cutoff values on the immunoassay are likely too low to detect any use of fentanyl and alprazolam.

C. Fentanyl and alprazolam may not be detected on a standard urine immunoassay.
D. The immunoassay would only detect chronic use of these substances.
E. The immunoassay should be repeated to ensure accuracy of results.

Correct answer: C. Fentanyl and alprazolam may not be expected to be positive on a standard urine immunoassay.

Explanation: Synthetic opioids (such as fentanyl) and certain benzodiazepines (lorazepam, alprazolam, clonazepam) are unlikely to be detected on standard immunoassays that were developed for morphine and diazepam. While diversion may be a concern, we can't rule out this patient is not taking these medications. A substance-specific test via GCMS should be performed. For alprazolam, the clinician can consider lowering the limit of detection in the laboratory or adding an enzyme to the urine sample to convert the undetectable metabolite to the parent drug as well.

5. A 41-year-old female presents as a follow up to the clinic. Her routine urine drug screen immunoassay shows a positive result for amphetamine. The patient states that she has been ill with a sinus infection and has been taking amoxicillin, pseudoephedrine/cetirizine combination, and dextromethorphan. The patient is adamant that she did not use any amphetamine or methamphetamine products. What is the most appropriate action for the clinician regarding the positive UDS?
A. Discontinue the patient from the treatment program for violating the substance use agreement
B. Ignore the results since the patient is taking several medications which can cause a false positive
C. Order confirmatory GCMS testing since dextromethorphan can cause a false positive for amphetamines
D. Order confirmatory GCMS testing since Amoxicillin can cause false positive for amphetamines
E. Order confirmatory GCMS testing since pseudoephedrine can cause false positive for amphetamines

Correct answer: E. Order confirmatory GCMS testing since pseudoephedrine can cause false positive for amphetamines

Explanation: Amphetamine immunoassays can have many false positives, and pseudoephedrine is one of them. Amoxicillin and dextromethorphan do not cause false positives for amphetamines. While there is a plausible cause for the positive result, confirmatory testing should be conducted to ensure this wasn't a true positive result.

References

1. Moeller KE, Kissack JC, Atayee RS, Lee KC. Clinical interpretation of urine drug tests: what clinicians need to know about urine drug screens. Mayo Clin Proc. 2017;92(5):774–96.
2. US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration. Mandatory guidelines for federal workplace drug testing programs: notices. Federal Register. 82. 2017;13:7920–70.

3. Nelson ZJ, Stellpflug SJ, Engebretsen KM. What can a urine drug screening immunoassay really tell us? J Pharm Pract. 2016;29(5):516–26.
4. Verstraete AG. Detection times of drugs of abuse in blood, urine, and oral fluid. Ther Drug Monit. 2004;26(2):200–5.
5. Cook JD, Caplan YH, Lodico CP, Bush DM. The characterization of human urine for specimen validity determination in workplace drug testing: a review. J Anal Toxicol. 2000;24(7):579–88.
6. Pesce A, West C, Egan city K, Strickland J. Interpretation of urine drug testing in pain patients. Pain Med. 2012;13(7):868–85.
7. Hull MJ, Bierer MF, Griggs DA, Long WH, Nixon AL, Flood JG. Urinary buprenorphine concentrations in patients treated with suboxone as determined by liquid chromatography-mass spectrometry and CEDIA immunoassay. J Anal Toxicol. 2008;32(7):516–21.
8. Danso D, Langman LJ, Jannetto PJ. Targeted opioid screening assay for pain management using high-resolution mass spectrometry. Methods Mol Biol. 1872;2019:41–50.
9. Fang WB, Chang Y, Mccance-katz EF, Moody DE. Determination of naloxone and nornaloxone (noroxymorphone) by high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry. J Anal Toxicol. 2009;33(8):409–17.
10. Jones AW. Pharmacokinetics of ethanol - issues of forensic importance. Forensic Sci Rev. 2011;23(2):91–136.
11. Tavakoli HR, Hull M, Michael Okasinski L. Review of current clinical biomarkers for the detection of alcohol dependence. Innov Clin Neurosci. 2011;8(3):26–33.
12. Cone EJ, Bigelow GE, Herrmann ES, et al. Non-smoker exposure to secondhand cannabis smoke. I. Urine screening and confirmation results. J Anal Toxicol. 2015;39(1):1–12.
13. Arntson A, Ofsa B, Lancaster D, Simon JR, Mcmullin M, Logan B. Validation of a novel immunoassay for the detection of synthetic cannabinoids and metabolites in urine specimens. J Anal Toxicol. 2013;37(5):284–90.
14. Vine MF, Hulka BS, Margolin BH, et al. Cotinine concentrations in semen, urine, and blood of smokers and nonsmokers. Am J Public Health. 1993;83(9):1335–8.

3 Epidemiology, Genetics, and Neurobiology of Substance Use and Disorders

Kristopher A. Kast and Jonathan Avery

High-Yield Review Points

- The 12-month prevalence of any SUD in the United States has remained relatively stable across time, representing 10–15% of the general population, with tobacco, alcohol, cannabis, and opioid use disorder being most common.
- Tobacco and underage alcohol use have declined over the past two decades, but cannabis use and use disorder have risen, alongside a rise in heavy alcohol use among women aged 12–20 years (closing the historical gender gap).
- Only a minority of individuals with SUD (19.3% in 2017) received any addiction treatment, marking a significant treatment gap.
- Addiction is a highly heritable (40–70% in family and twin studies), polygenic disorder with multiple risky genes of small effect size that interact with environmental influences (gene-by-environment interactions) and epigenetic mechanisms (including histone modification, DNA methylation, and microRNA regulation) to produce the syndrome of a substance use disorder.
- The three-stage addiction cycle of binge intoxication, withdrawal/negative affect, and craving correspond to specific neuroanatomical substrates (the

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striatum, extended amygdala, and prefrontal cortex, respectively). Each of these involves complex neurocircuitry that govern:

- Compulsive behavior (cortico-striatal-pallidal-thalamic-cortical feedback loops)
- Hedonic reward (mesolimbic dopaminergic system)
- Homeostatic antireward (allostatic change of the mesolimbic dopaminergic firing rate and activation of the stress-response neurotransmitter systems, including CRF, dynorphin, and norepinephrine)
- Prefrontal Go/Stop systems (cholinergic projections from the anterior cingulate and dorsolateral prefrontal cortex, and orbitofrontal and ventrolateral prefrontal cortex)

Introduction

Addiction is a complex, chronic, relapsing neuropsychiatric disorder with genetic and epigenetic risk, conserved common neuropathology, significant prevalence across populations, severe medical and psychiatric comorbidity, and social and occupational impairment with resulting large individual and societal cost. This chapter will focus on (1) the epidemiology of substance use, unhealthy use, and use disorder; (2) genetic and epigenetic risk and resilience for addiction; and (3) the common neuropathology of the three stages of the addiction cycle. This chapter offers a number of perspectives that translate the historically moralized and stigmatized clinical syndrome of addiction into the language of medicine and psychiatry. In addition, it reviews clinically useful data that argues against culturally prevalent stigma toward patients with these life-threatening disorders.

Epidemiology of Substance Use, Unhealthy Use, and Use Disorder

Substance Use Disorders

The prevalence of alcohol and illicit substance use disorders among Americans aged >12 years was 7.2% in 2017 (exclusive of the 10.2% prevalence of daily tobacco use) [1]. For reference, this is roughly equivalent to the prevalence of major depression among adult Americans over the same period (7.1% in 2017) [1]. The majority of those with any SUD have tobacco or alcohol use disorder (10.2% and 5.3%, respectively), while 2.8% have an illicit drug use disorder. The most common illicit drug use disorder is cannabis use disorder (1.5% of the general population), with opioid use disorder second most prevalent (0.6% using prescription opioids; 0.2% using heroin). The remaining substance categories occur at <1% prevalence.

Substance use disorder prevalence has been relatively stable over time, with consistent reports of 10–15% over the past two decades, though differences in samples, diagnostic instruments, and data collection across different national surveys contribute to some variability in findings [2, 3]. For example, the 2012–2013 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) found a 13.9% 12-month prevalence of alcohol use disorder, though this sample includes only those individuals >18 years old (compared to the finding of 5.3% in the 2017 National Survey of Drug Use and Health, which collects data for those aged >12 years) [1, 4]. Table 3.1 reviews the four major national surveys of SUD and related conditions, comparing their data collection periods, sample sizes, differences in inclusion criteria, and diagnostic instruments.

Substance Use and Recent Trends

Substance use (without the addiction syndrome) is far more common than substance use *disorder*. Alcohol is the most commonly used substance in the United States, with 140.6 million current (i.e., "past month") users in 2017 (51.7% of the general population aged >12 years) [1]. Tobacco products are second, with 48.7 million current users (17.9%). Cannabis is third, with 26 million current users (9.6%). Opioids are fourth, with 3.7 million current past month users (3.2 million using prescription opioids; 0.5 million using heroin), accounting for 1.4% of the general population; 11.4 million Americans have used any opioid in the past year (4.2% of the population), highlighting the episodic nature of use for most. The remaining substance categories (cocaine, hallucinogens, inhalants, and other prescription psychotropics) each have <1% of the general population as current past month users.

Noteworthy epidemiological trends in substance use over the past two decades include (1) a decline in tobacco users from 26% in 2002 to 17.9% in 2017, (2) a decline in underage alcohol use from 28.8% of 12–20-year-olds in 2002 to 19.7% in 2017, and (3) a rise in cannabis use from 6.2% in 2002 to 9.6% in 2017 (driven by increased use among >18-year-olds). The substances with the most new users in 2017 are alcohol (4.9 million), cannabis (3 million), prescription opioids (2 million), and tobacco (1.9 million).

Unhealthy Substance Use

Addiction (or substance use disorder) is more clearly defined than *unhealthy* use, the latter being an umbrella term for any substance use above *low or lower risk* use [5]. Unhealthy use includes the entire spectrum of substance use associated with any health consequences, including substance use disorder (or addiction), harmful use (or use that has led to specific health consequences for an individual; e.g., alcohol intoxication that has resulted in a fall with bone fracture), and hazardous or at-risk use (or an amount of use known to increase the risk of adverse health

Table 3.1 Major cross-sectional surveys studying prevalence of substance use disorders in the United States

Survey name	Dates of data collection	Population size surveyed	Representativeness of the sample	Diagnostic instrument used	Data reported	Notable findings
NIMH Epidemiologic Catchment Area (ECA)	1980–1984	$n = 20{,}000$	5 metropolitan catchment areas in the United States	Diagnostic Interview Schedule (DSM-III criteria)	Incidence and service-use data for all psychiatric disorders, including SUD	First attempt at a nationally-representative sample
National Comorbidity Survey	1990–1992; 2001–2002	$n = 9{,}000$	Nationally representative sample (though smaller than later surveys); ages 15–54 (younger sample than other surveys)	Composite International Diagnostic Interview (modified; DSM-III-R criteria)	Lifetime and 12-month prevalence data for SUD and psychiatric disorders	Lifetime prevalence of any SUD was 35% (tobacco 29%; alcohol 13%; illicit drug 8%); 12-month prevalence of any SUD was 13% (tobacco 11%; alcohol 3%; illicit drug 1.4%)
National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)	2001–2002; 2004–2005; 2012–2013	$n = 43{,}000$ in 2004–2005 survey; $n = 36{,}000$ in 2012–2013	Nationally representative sample; ages 18 and older	Alcohol Use Disorder and Associated Disabilities Interview Schedule (DSM-IV criteria)	Lifetime and 12-month prevalence data for SUD and psychiatric comorbitidy; also collected saliva DNA samples from participants in most recent sample	Closing gender gap between men and women for alcohol use disorders; significant comorbidity of SUD and mood, anxiety, and personality disorders; significant treatment gap (only 19.8% of those with lifetime alcohol use disorder were ever treated)
National Survey on Drug Use and Health (NSDUH)	Conducted annually since 1971; most recent data from 2017	$n = 70{,}000$ in most recent survey	Randomly selected national sample; ages 12 and older	In-person interview; NSDUH-specific instrument	Prior year prevalence of substance use and use disorder, as well as psychiatric comorbidity	Most recent data are summarized in the chapter text

This table presents the four nationally representative epidemiological surveys conducted in the United States since 1980. The dates of data collection, sample size, unique features of the sample, diagnostic instruments, data reported, and important findings are reviewed

consequences, such as *heavy* alcohol use). The concept of *unhealthy* use captures any and all conditions related to substance use that warrant targeted interventions (whether preventive or therapeutic), including those states that do not (yet) meet diagnostic criteria for substance use disorder.

For most substances, no amount of use is known to be completely safe, and single episodes of intoxication may risk sequelae (e.g., myocardial infarction with first cocaine use); thus, any amount of use may be hazardous or at-risk. Alcohol is a notable exception, where *heavy use* known to increase risk of adverse health outcomes has been defined using epidemiological data; these are 5 or more standard 12-gram drinks in a day or >14 drinks per week for men; these amounts are adjusted to 4 or more drinks per day or 7 per week for women or men aged >65 years [5]. In 2017, 24.5% of the general population aged >12 years endorsed drinking 5 or more drinks in a day, with a notable peak among 18–25-year-olds (36.9% of this age group) [1]. Notably, alcohol use under these levels may still be hazardous or harmful, as intoxication may occur with less intake and result in impaired functioning and injury.

Transition from Substance Use to SUD

Of individuals who have ever used certain substance categories, relatively few develop addiction. The highest rates of conversion from "ever used" to SUD occur for tobacco (14%), heroin (10%), alcohol (7.8%), prescription opioids (5.2%), cannabis (3.8%), and cocaine (2%) [2]. The proportion of current past year users who have a SUD differs across substance categories; some, like heroin, prescription opioids, and tobacco, have >50% of current users with an associated SUD, whereas current cannabis and alcohol users are less likely (15% and 10%, respectively) to have a current SUD. Risk of developing SUD is elevated in individuals who initiate use in adolescence, with subsequence development of SUD in 34% of those whose first use occurred <14-years-old (vs. 14% with first use >21 years old) [2].

The Closing Gender Gap

Historically, women have been less likely to use alcohol and illicit substances, leading to greater SUD rates among men (rates of use and SUD among men have been consistently twice that found among women) [3]. However, this gender gap has not been static in the United States; in more recent studies, women aged 12–20 years have greater rates of heavy alcohol use than age-matched men. Further, the likelihood of transitioning from substance use to addiction is equal for men and women, leading to the increasing concern that the historical gender gap, likely related to cultural norms, is closing [6]. This is especially important given the increased risk for negative health and reproductive or perinatal outcomes for women with smaller amounts of alcohol, compared to men.

Culture, Race, Ethnicity, Immigration, and SUD

Differences in rates of SUD exist across racial and ethnic groups in the United States [7]. Native Americans have elevated rates of SUD compared with the general population (12.2% vs. 7.2% in 2017); Asian Americans have lower rates (3.7%); Black Americans have similar rates of any use disorder, though elevated rates of illicit substance use disorder at 3.4%; Latino Americans, native Hawaiians, and Pacific Islanders have rates comparable to national averages. However, even for populations with relatively similar rates of SUD, there are disparities in medical and psychiatric sequelae; as an example, Black Americans experience higher mortality from alcohol use disorder than white Americans despite similar prevalence, though socioeconomic status may be a confounding variable [3]. Additionally, increasing attention has been paid to disparities in criminal justice system involvement for racial minorities with SUD [3].

Populations immigrating to the United States generally have lower risk of SUD than native-born Americans, though risk normalized with duration of residence >10 years [8]. Among more disadvantaged immigrant populations (undocumented Mexican groups being most frequently studied), alcohol, tobacco, and illicit drug use are elevated compared with both American and control populations in the home country; in one sample, 42.3% of Mexican migrants report at-risk alcohol use, 31.4% smoke tobacco, and 17.7% use illicit substances [9].

Further, cultural norms for low-risk alcohol use (and perhaps for other substances) differ markedly internationally, leading to large geographical differences in reported prevalence of alcohol use disorder despite using standardized SUD diagnostic criteria. Among European countries, estimated prevalence of alcohol use disorder in 2010 ranged between <1% (in Italy and Spain) and > 12% (in Latvia)—though the per capita consumption only varied threefold; further, reported use in countries with religious prohibition against alcohol consumption leads to markedly elevated per capita consumption rates, most likely representing underreporting of individual use [10].

The Treatment Gap for SUD

Of individuals with SUD in the United States, only 19.3% received any treatment (and only 12.2% received treatment in a specialty facility); this marks a significant treatment gap. Of those who do not receive needed treatment, only 5.5% perceive a need for treatment, highlighting an important attitudinal barrier to accessing care. Of those who do believe they need treatment, 40% are not ready to stop using; 33% had no health insurance and were unable to pay for treatment [1].

Comorbidity

SUDs are highly comorbid with psychiatric disorders, often complicating treatment and prognosis. The 2017 prevalence of any mental illness was 18.9% of Americans >18 years old (4.5% of all adults having serious mental illness or SMI) [1]. 3.4% of

all Americans >18 years old experienced comorbid SUD and any other psychiatric disorder (with 1.3% having SUD and SMI). Among all individuals with SUD, 45.6% had any mental illness (much higher than the 16.7% occurrence of mental illness among Americans without SUD). Among all individuals with mental illness, 18.5% have SUD (again, higher than the 5.1% of Americans without mental illness who have SUD). Affective, anxiety, personality, and psychotic disorders, as well as attention-deficit hyperactivity disorder (ADHD), are the most common comorbid psychiatric disorders in patients with SUD; 15–25% of individuals with SUD have comorbid ADHD (and 10–45% of those with ADHD have a SUD), 20–29% have comorbid mood or anxiety disorders, and 30–40% have comorbid personality disorders (most commonly antisocial, histrionic, or dependent) [2, 11]. Comorbid SUD among individuals with schizophrenia is markedly elevated, reaching 50% lifetime prevalence; 60–90% use tobacco, with 28% having a nicotine use disorder, and rates of other SUD range from 20% to 65% [12].

Among adolescents aged 12–17 years, 13.3% experienced a major depressive episode in 2017; these depressed adolescents experienced elevated rates of tobacco (0.8% vs. 0.3% daily smokers), alcohol (1.2% vs. 0.6% heavy drinkers), and illicit drug use (29.3% vs. 14.3% using any illicit substance, most commonly cannabis) over the same year, with 10.7% meeting criteria for any SUD (compared to 2.9% of adolescents having SUD who did not experience a major depressive episode in 2017) [1].

Consequences of Use

SUD has adverse effects on nearly every organ system. Infectious disease transmission, particularly for viral hepatitis and HIV, is a serious consequence of intravenous drug use (IVDU), with 6–9% of new HIV cases in 2016 associated with IVDU [13]. Further, the incidence of new hepatitis C viral infections has doubled between 2004 and 2014 in the United States, mirroring an associated rise in admissions for injection opioid use over the same period [14].

Despite increased rates of SUD remission during pregnancy (ranging from 70% to 90% for illicit drugs and alcohol; around 30% for tobacco), 5–15% of pregnant women continue to use substances in the United States (5.9% use illicit drugs, 8.5% drink alcohol, and 15.9% smoke tobacco) [15]. Adverse obstetrical and neonatal outcomes associated with substance use include fetal mortality, congenital anomalies, preterm delivery, low birthweight, neonatal abstinence syndrome (for opioid-exposed newborns), and neurodevelopmental disorders (including fetal alcohol syndrome). Six neonates have neonatal abstinence syndrome, and 9 have fetal alcohol spectrum disorders for every 1000 live births in the United States [16]. Additionally, high rates of postpartum SUD relapse for mothers lead to deficits in the caregiving environment for infants, risking neglect and sudden infant death syndrome.

Overall, SUD-related deaths have doubled since 2000 [17]. Specifically, deaths from drug overdose in the United States have risen dramatically since 2000, reaching a peak of over 72,000 in 2017 (from <20,000 deaths in 2000) [6]. These overdoses have

largely been driven by increasing rates of fentanyl contamination of the nonprescription drug supply and "prescription" opioids, with 49,000 overdose deaths in 2017 involving these drugs. For every opioid overdose death, there are >20 emergency department visits related to opioid use disorder [16]. Emergency department (ED) visits related to substance use have increased in parallel with the opioid epidemic (doubling between 2004 and 2011, reaching 1,626 ED visits per 100,000 population) [18].

Genetics and Epigenetics of SUD

Genetic Risk for SUD

Family and twin studies demonstrate that substance use disorders (SUDs) have significant heritability, with complex genetic influence accounting for 40–70% of the variation in the phenotypic expression of addictive behavior [2, 19]. Addiction is a polygenic disorder, with the relatively large cumulative genetic risk being a sum of multiple "risky" genetic alleles, each with a small individual effect size. This means that the genetics of addiction are non-Mendelian (i.e., there are no dominant, recessive, or X-linked patterns of intergenerational transmission) and that no single gene fully determines whether an individual will develop SUD. Genetic influences appear to be most important for progressing to (and maintaining) substance dependence, though there is some evidence for limited effects on initiation and early use [20].

Exemplar Genes

Hundreds of specific genetic loci associated with risk of SUD have been identified using candidate gene and genome-wide linkage and association studies [20]. Not all have been replicated. Heuristically, we can categorize these genes by their function in (1) substance-specific metabolism, (2) addiction-related neurocircuits, and (3) those requiring further study to understand their relationship to SUD pathogenesis.

Genes Implicated in Substance Metabolism

Genes encoding proteins involved in substance metabolism may affect the amount of a psychoactive substance available to the central nervous system (CNS) or may be involved in the clearance of toxic metabolites. The alcohol dehydrogenases (including ADH1A, 1B, and 1C, ADH4, ADH5, and ADH7) have been identified across genetic studies as affecting risk of developing alcohol use disorder [19]. ADH converts alcohol into acetaldehyde, a toxic intermediate that leads to an aversive "flushing" response. Increased ADH function or decreased acetaldehyde dehydrogenase (ALDH2) function (the latter a phenotype commonly found in Asian populations), both lead to accumulation of acetaldehyde and the aversive reaction, which appears to reduce the risk of developing alcohol use disorder.

Genes Implicated in Addiction-Related Neurocircuits

Genes involved in neurotransmitter systems known to be associated with the neurobiology of addiction have also been implicated. The GABAA receptor gene cluster (specifically, GABRA2) modulates risk of developing alcohol use disorder via anxiety-related phenotypes and sensitivity to the hedonic effects of alcohol consumption [19]. Glutamatergic pathways (specifically CNIH3, involved in ionotropic AMPA-receptor conductance) have been associated with opioid use disorder in genome-wide association studies, or GWAS (a study design that uses markers of genetic variation across the genome to compare cases and controls, identifying specific genetic loci associated with a specific diagnosis) [20]. Nicotinic cholinergic receptors (including alpha-5 and beta-3, CHRNA5 and B3) are associated with nicotine use disorder, amount of daily cigarette consumption, vulnerability to tobacco smoking in schizophrenia, and development of lung cancer [16, 19]. The mu opioid receptor (specifically OPRM1) has been implicated in the pathogenesis of multiple SUDs, with an A118G polymorphism (encoding Asn40Asp amino acid substitution) leading to functional differences in the opioid receptor that appear to confer risk of progressing to SUD, especially in Asian populations where the allele is most common [19]. Single-nucleotide polymorphisms, or SNPs (a single DNA base pair at a specific chromosomal locus that is polymorphic across a population, serving as an easily identifiable surrogate marker to compare large quantities of genetic material between cases and controls in a study), associated with the kappa opioid receptor (responsible for aversive effects; encoded by OPRK1) and its ligand prodynorphin (encoded by PDYN) have also been associated with alcohol use disorder.

The dopamine D2 receptor (DRD2), given its function in the reward system circuit, has been intensively studied, but significant controversy exists around the findings [19]. DRD2 has been associated with multiple SUD phenotypes, but it is unclear if the association is due to this locus or nearby cytoskeletal genes.

Finally, voltage-gated potassium channel (KCNC1, G2, A4) and calcium-dependent signaling (phosphatidylinositol transport gene PITPNM3) genes important for long-term potentiation have been associated with opioid use disorder, linking neural correlates of learning to SUD development.

Genes with Unknown SUD-Related Function

GWAS have identified a number of genetic loci linked to SUD with unclear function in the pathogenesis of addiction, though these offer promising leads for novel pathways in SUD neurobiology. The family with sequence similarity 53, member B (FAM53B) and cyclin-dependent kinase 1 (CDK1) are associated with cocaine use disorder; autism susceptibility candidate 2 (AUTS2), serine incorporator 2 (SERINC2), and chromosome 15 open reading frame 53 (C15orf53) are associated with alcohol use disorder [19].

Gene-by-Environment Interaction

Known additive genetic influences alone, like those loci reviewed above, account for a only a small proportion of the total variance in SUD. Thus, the interaction between genetic influence and environmental exposures has been studied to account for further risk affecting development of SUD.

Early studies of gene-by-environment interactions focused on the hypothalamic-pituitary-adrenal (HPA) axis, given the role of activation of this system and its corticosteroid mediators in response to environmental stress. The serotonin transporter polymorphic region, or 5-HTTLPR short allele, known to mediate risk of depression in relation to stressful life events also affects risk of SUD. The short allele possesses a glucocorticoid response element in its promoter region (allowing for HPA-axis-mediated stress response) and has been found to mediate risk of heavy drinking and unprescribed drug use in homozygous individuals with multiple negative life events [20].

Additionally, the genetic risk of tobacco smoking attributable to CHRNA5 (nicotinic cholinergic receptor, alpha-5 subunit) has been shown to be modulated by parental monitoring and exposure to peer tobacco use, again demonstrating a gene-by-environment interaction [20].

Epigenetic Influences

Epigenetic mechanisms are influences on DNA transcription and protein expression that are not encoded in the genetic sequence. These include (1) reduction in gene expression via methylation of specific genetic loci; (2) histone modification via acetylation, impacting availability of genetic loci for transcription; and (3) microRNA regulation of protein translation. Given the significant proportion of risk for SUD not accounted for by genetic variance, epigenetic mechanisms may play an additional role.

Candidate gene methylation studies have demonstrated differential methylation of genes associated with major and minor neurotransmitter systems (monoamines including dopamine and serotonin, cannabinoid, and opioid systems) as well as drug metabolism (CYP2D6 involved in nicotine metabolism; COMT for catecholamines) for alcohol- and nicotine-dependent individuals [20].

Histone modifications via acetylation (making genetic loci available for transcription) and deacetylation (preventing transcription) lead to brain region and cell type-specific changes that are longer lasting and may play roles in neuroadaptations that lead to alcohol withdrawal effects [20].

MicroRNA expression in the brain affects synapse development and neuronal plasticity in response to substance exposure. These effects are mediated by adaptation responses in neurotransmitter systems, cytoskeletal organization, and regulation of transcription. For example, the mRNA of neuronal voltage-gated potassium channel BK decreases rapidly following exposure to alcohol, an effect

mediated by the microRNA miR-9 [20]. Further microRNAs have been identified that regulate dopamine receptor (miR-382 and D1 receptor) and brain-derived neurotrophic factor (miR-206 and BDNF) expression [20].

Relevance to Treatment

Individual genetic differences are important in understanding differential treatment response in SUD. Response to naltrexone for alcohol use disorder may be modulated by the OPRM1 Asp40 allele (though this difference appears to be overcome by additional treatment modalities) [21]. Response to interventions for nicotine use disorders is highly heritable (40–60% heritability in twin studies), and GWAS have identified multiple genes associated with successful smoking cessation, with the further finding that those who respond to bupropion and nicotine replacement appear to differ genetically [22].

Of relevance to opioid use disorder treatment, the half-life of methadone ranges from 5 to 130 hours (mean of 22 hours) between individuals; this pharmacokinetic variability is mediated by differences in hepatic CYP enzyme function. Methadone's metabolism is complex, involving multiple CYP enzyme subtypes with different effects on the S- and R-enantiomers present in racemic methadone and multiple active and inactive methadone metabolites produced. CYP2B6 is responsible for a great proportion of methadone clearance, and there are 38 CYP2B6 protein variants with different catalytic activity and expression across studied populations (with a 300-fold inter-individual variability) [23]. CYP2D6 also participates in methadone metabolism and exhibits phenotypic variability in methadone clearance across ultra-rapid and poor metabolizers [23]. Although the pharmacogenomics have yet to be fully characterized, we can expect that some individuals (e.g., those with the CYP2B6∗4 SNP) may require higher doses of methadone to overcome rapid hepatic clearance of methadone, while others with slower clearance may require lower methadone doses to avoid respiratory depression (from R-methadone's agonism of the mu opioid receptor) or cardiac arrhythmia (due to the blockade effect of S-methadone on voltage-gated potassium channels in cardiac tissue).

Neurobiology of SUDs

Tripartite Addiction Cycle and Associated Neuroanatomy and Circuitry

The dominant contemporary neurobiological model of addiction consists of three stages: (1) binge/intoxication, with associated classical conditioning to drug-related cues; (2) withdrawal/negative affect; and (3) craving (preoccupation/anticipation) [2, 16]. Three major neuroanatomical regions are known to be

important in each stage of the addiction cycle: (1) the striatum (binge/intoxication stage), (2) the extended amygdala (withdrawal/negative affect stage), and (3) the prefrontal cortex (craving stage).

Binge/Intoxication Stage and the Striatum

Habitual or compulsive behavior is encoded in extrapyramidal motor circuits involving the basal ganglia. These are looped feedback motor systems linking cortical to striatal to pallidal to thalamic, then back to cortical neurons [2]. The role of the striatum in this circuit is important for in the binge/intoxication stage of the addiction cycle.

The striatum is anatomically composed of the caudate and putamen; it can be divided into dorsolateral (with predominantly motor input) and ventromedial (largely limbic input) areas; the ventromedial striatum includes the nucleus accumbens (NAc), which mediates the hedonic/rewarding effects of psychoactive substance intoxication in addiction.

The classical mesolimbic reward system requires activation of midbrain dopaminergic neurons in the ventral tegmental area (VTA) that project to the NAc; cocaine and other stimulants lead to increased dopamine release from VTA axon terminals in the NAc [2]. Nicotine activation of a4b2 acetylcholine receptors also modulates dopaminergic activity in the mesolimbic circuit [2]. Opioids, agonizing mu opioid receptors, disinhibit firing of VTA dopaminergic neurons in the NAc (by inhibiting inhibitory GABAergic interneurons) and also act independently of the mesolimbic system, directly agonizing mu opioid receptors in the NAc. Alcohol's reinforcing effect is complex, but appears to in part involve enhancement of GABAA receptor function, which also disinhibits mesolimbic dopaminergic firing. Phencyclidine may inhibit postsynaptic glutamatergic NMDA receptors in the NAc. Cannabinoids agonize CB1 receptors, which modulate both dopamine and opioid activity in the NAc [2]. Figure 3.1 illustrates these sites of action for each substance class.

NAc activation initially reinforces substance use (bingeing) and also strengthens classically conditioned associations between substance-induced reward and previously neutral stimuli (paraphernalia, location of use, etc.) paired with the substance. The conditioned stimuli then are able to independently induce dopaminergic firing in the NAc, resulting in "incentive salience" and motivation to repeat use (as occurs in the craving characterizing the third preoccupation/anticipation stage) [2, 16].

Withdrawal/Negative Affect Stage and the Extended Amygdala

With repeated substance-induced NAc activation, dopamine release and response in the NAc is attenuated; dopamine D2 receptor density and basal firing rate of mesolimbic dopaminergic neurons decrease with repeated substance exposure [2]. This is thought to be mediated by an opponent-process counter-adaptation in the "anti-reward" system that is in homeostatic balance with the reward system. The introduction of NAc activation by substance intoxication leads to an allostatic shift (or move to homeostasis) in the set point (i.e., the basal dopaminergic firing rate is stably lower than before repeated substance exposure, finding a new homeostatic

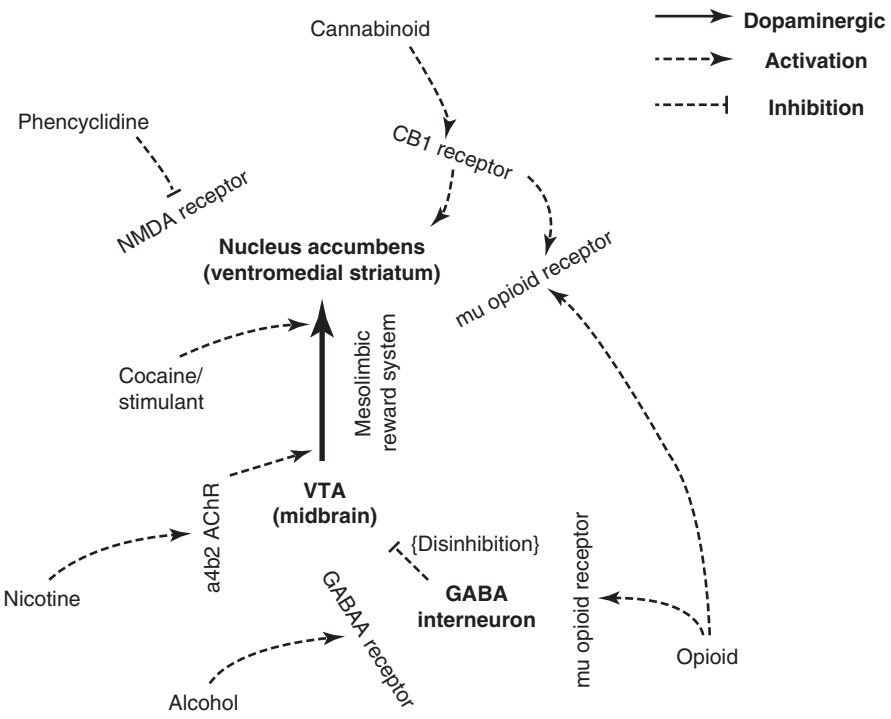

Fig. 3.1 Substance-specific effects on the classical mesolimbic reward system. Dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) in the ventromedial striatum compose the mesolimbic reward system, important for the rewarding effects of substance intoxication. Cocaine and other stimulants increase dopamine release from VTA axon terminals in the NAc; nicotine activation of a4b2 acetylcholine receptors in the VTA modulates its dopaminergic activity; opioids agonize mu opioid receptors and disinhibit firing of VTA dopaminergic neurons in the NAc by inhibiting inhibitory GABAergic interneurons and also directly agonize mu opioid receptors in the NAc; alcohol's reinforcing effect involves enhancement of GABAA receptor function, which disinhibits VTA dopaminergic firing; phencyclidine inhibits postsynaptic glutamatergic NMDA receptors in the NAc; cannabinoids agonize CB1 receptors, which modulate both dopamine and opioid activity in the NAc

equilibrium or allostasis), thought to be driven by neuroplastic adaptation involving glutamatergic projections from the amygdala and prefrontal cortex to NMDA and AMPA receptors in the mesolimbic system [2]. This reduction in mesolimbic dopaminergic activity secondarily decreases sensitivity to reward from natural reinforcers (food, sex, etc.), as well.

The homeostatic anti-reward system drives the withdrawal/negative affect stage of the addiction cycle, consisting of a state of dysphoria, anhedonia, stress sensitivity, and anxiety. It involves the central division of the extended amygdala, a circuit composed of the amygdala's central nucleus, bed nucleus of the stria terminalis, and a transition zone in the NAc shell [2]; the habenula has also been implicated more recently [16]. The withdrawal/negative affect stage signals a shift from positive to negative reinforcement as the dominant motivator of addictive behavior; in this

stage, seeking relief from the aversive negative emotional state is most salient. The extended amygdala activates stress-response neurotransmitter systems, including corticotropin-releasing factor (CRF), norepinephrine, and dynorphin, which drive the aversive withdrawal state.

Craving (Preoccupation/Anticipation) and the Prefrontal Cortex

As noted above, the craving stage is marked by conditioned stimulus-induced release of dopamine in the NAc, motivating compulsive drug-seeking behavior. The prefrontal cortex's executive function manages this cue-induced impulse using two opposing systems, termed the Go system (which engages automatic habitual behavior) and Stop system (which inhibits these habitual behaviors) [2]. The Go system is composed of the anterior cingulate and dorsolateral prefrontal cortex, both involved in attention, planning, and self-initiation; the Stop system involves the orbitofrontal cortex and ventrolateral prefrontal cortex, which participate in response inhibition, rule generation, set-shifting, and salience attribution, integrating anticipated reward or punishment [2].

Prefrontal glutamatergic projections from these systems to the VTA and striatum modulate the response to craving, whether it is cue-induced anticipation of reward or withdrawal-induced desire for relief [16]. In the addiction syndrome, the Stop system is hypofunctional, and the Go system is hyperactive alongside a sensitized anti-reward system [2, 16]. This imbalance leads to a great disadvantage for individuals with SUD working to oppose impulses toward relapse.

Neurodevelopment during Adolescence

Ongoing neurodevelopment in adolescence (extending into the third decade of life) implies greater neuroplasticity in this age group than is present in adulthood; this allows for more rapid neuroadaptation to psychotropic substance exposure, and thus faster development of an addiction syndrome [16]. The rate of neurodevelopment is uneven across different circuits, with maturity achieved in the reward-mediating (striatal) and emotional (limbic) systems earlier than the top-down cognitive control circuits of the prefrontal cortex [16]. This leads to greater affective reactivity and reward-seeking behaviors without the (later-to-develop) self-regulation of impulses or exciting risk.

Increased risk-taking and impulsivity, coupled with greater neuroplasticity, are thought to create a uniquely vulnerable period for the development of SUD in adolescence and emerging adulthood.

Summary of Relevant Neurotransmitter Systems

Monoamines play an important role in addiction. Dopamine is predominant, acting on D1 and D2 receptors in the mesolimbic and mesocortical dopaminergic circuits

mediating reward and motivation (as discussed above); the nigrostriatal dopaminergic circuit is part of the extrapyramidal motor system, which may also become dysregulated by substance exposure (e.g., emergent stereotypy in stimulant use disorder). Serotonin modulates the dopaminergic system in addiction. Norepinephrine, acting on a1, a2, and b adrenergic receptors from noradrenergic projections out of the locus coeruleus in the dorsal pons, is involved in the stress response, as well as attention/vigilance and arousal.

The opioid system has three receptors, most importantly mu (mediating euphoria, analgesia, and respiratory drive) and kappa (mediating dysphoria and neuroendocrine stress response); both mu and kappa are implicated in the addictive syndrome. The endocannabinoid receptor, CB1, modulates both the opioid and dopamine systems.

Excitatory glutamatergic input from the cortex and inhibitory GABAergic interneurons also feed into addiction-related circuits, with some substances acting directly on these systems (e.g., phencyclidine blocking NMDA glutamate receptors; alcohol enhancing GABAA receptor activity).

Additional neurotransmitters have been implicated in the stress response system, including corticotropin-releasing factor (CRF acting at CRF1 and CRF2 receptors), vasopressin (V1b receptors), neuropeptide Y (Y1 and Y2 receptors), and nociceptin/orphanin FQ (opioid receptor-like 1, or ORL-1 receptors).

Review Questions

You are evaluating a new patient who endorses alcohol and tobacco use on a screening questionnaire; given the frequent co-occurrence of illicit substance use, you begin to formulate additional questions for the patient, informed by current epidemiological data.

1. Tobacco and alcohol are the most common substances associated with a use disorder (with current 12-month prevalences around 10% and 5%, respectively). What illicit substance has the greatest 12-month prevalence of use disorder?
   A. Cannabis
   B. Opioid
   C. Stimulant (including cocaine)
   D. Hallucinogen
   E. Benzodiazepine

   Answer: A

   Explanation: Cannabis, with a 12-month prevalence of 1.5%; opioid use disorder is the second most prevalent of the illicit substances (0.6% using prescription opioids; 0.2% using heroin). The remaining substance categories occur at <1% prevalence.

2. After alcohol (with 4.9 million new users in 2017), what two substances have the most new users (or "initiates") in 2017?
   A. Tobacco and cannabis
   B. Prescription opioids and stimulants (including cocaine)
   C. Cannabis and prescription opioids
   D. Benzodiazepines and non-prescription opioids
   E. Cannabis and benzodiazepines

   Answer: C

   Explanation: Cannabis and prescription opioids, with three million and two million new users in 2017, respectively. Tobacco had 1.9 million new users in the same period, continuing a downward trend for tobacco users (declining from 28.8% to 19.7% of the population between 2002 and 2017).

Your new patient is a college-aged woman who endorses drinking "only occasionally," but reports at times having 4 or 5 12-ounce beers in an evening. You are considering how to effectively approach discussing this amount of alcohol use with the patient, using your understanding of the known health risks associated with specific amounts of alcohol exposure.

1. While most substances do not have a "safe" amount of use, alcohol has a specific amount of use that has been defined as *hazardous* or at-risk for adverse health outcomes. How many standard 12-gram drinks are considered "heavy" use for women and men aged >65 years?
   A. 5 or more drinks/day or >14 drinks/week
   B. 7 or more drinks/day or >21 drinks/week
   C. 2 or more drinks/day or >7 drinks/week
   D. 4 or more drinks/day or >7 drinks/week
   E. 2 or more drinks/day or >5 drinks/week

   Answer: D

   Explanation. 4 or more drinks/day or >7 drinks/week are considered *heavy use* for women or men >65 years. For men younger than 65 years, heavy use is 5 or more drinks/day or >14 drinks/week. Though these amounts are hazardous, drinking less quantities may still be unhealthy and lead to adverse health outcomes (such as injury during acute intoxication).
2. The "gender gap" refers to the historical finding of roughly twice the rates of alcohol and other SUD among men compared to women. In what population the observation of a closing gender gap is most pronounced?
   A. Heavy alcohol use among women aged 12–20 years
   B. Heavy alcohol use among women aged 20–35 years
   C. Opioid and cannabis use among women aged 12–20 years
   D. Opioid and cannabis use among women aged 20–35 years
   E. Alcohol and tobacco use among women aged 12–20 years

   Answer: A

Explanation: Heavy alcohol use among women aged 12–20 years now exceeds rates of age-matched men. This, coupled with the fact that the likelihood of transitioning from use to addiction is equal for men and women, indicates that the historical gender gap is closing for alcohol, and perhaps signals a cultural shift that may have similar effects for other SUD.

You identify an alcohol use disorder in a patient admitted to your general hospital's inpatient psychiatric unit. The patient reports that they have never discussed their drinking with a medical provider before, but they wonder aloud if their alcohol use has an effect on their mood states.

1. What percentage of individuals in the general population with a SUD received any treatment in 2017, according to NSDUH data?
   A. 40%
   B. 30%
   C. 20%
   D. 10%
   E. 5%

   Answer: C

   Explanation: 20% (actual number is 19.3%) of individuals with SUD received treatment in 2017; only 12.2% received treatment in a specialty facility. The roughly 80% of individuals with SUD who do not receive treatment indicate a significant treatment gap, a target for public health interventions.
2. SUD is highly comorbid with other psychiatric disorders, complicating treatment, and prognosis. What percentage of individuals with SUD have a psychiatric comorbidity? And what percentage of individuals with any psychiatric disorder have a SUD?
   A. 65% and 33%
   B. 45% and 20%
   C. 50% and 50%
   D. 20% and 45%
   E. 33% and 66%

   Answer: B

   Explanation: 45% of individuals with SUD have a comorbid psychiatric disorder; 20% (18.5% from NSDUH data) of individuals with a psychiatric disorder have a SUD. Both are above general population rates (16.7% of those without a SUD have any psychiatric disorder; 5.1% of those without a psychiatric disorder have a SUD).

Your patient reports that their mother received treatment in a methadone clinic during her pregnancy, though she relapsed postpartum and was incarcerated for drug-related charges in the patient's early childhood. The patient brings this up with you because they were just prescribed opioid pain medication following an outpatient surgical procedure, and they ask you if they can safely take the pills.

1. Addiction is a polygenic disorder, with each risky gene conferring a relatively small effect on the overall risk of developing the syndrome. Despite this, estimates of heritability (or the degree of variation in phenotype attributable to inherited genetic risk) in SUD are:
   A. 10–40%
   B. 20–50%
   C. 30–60%
   D. 40–70%
   E. 50–80%

   Answer: D

   Explanation: 40–70% heritability of SUD has been repeatedly demonstrated by family and twin studies. The genetics are non-Mendelian (without dominant, recessive, or X-linked patterns of transmission) and no single gene determines the development of SUD. The genetic risk appears most important for the progression from use to use disorder.
2. The interaction between genetic risk and environmental exposures influence individuals' risk of progressing to SUD. The 5-HTTLPR short allele contains a response element that mediates the risk of heavy alcohol and drug use in individuals with multiple negative life events; what is the biological mediator of this response element?
   A. Corticotropin-releasing factor (CRF)
   B. Corticosteroids
   C. Norepinephrine
   D. Dynorphin
   E. Serotonin

   Answer: B

   Explanation: Corticosteroids influence a corticosteroid response element in the promoter region of 5-HTTLPR "short" allele, serving as a link between stressful negative life events (which induce corticosteroid release) and risky genetic elements linked to SUD.

Your patient, a first-year college student, has found the biological disease model helpful in conceptualizing their newly diagnosed cannabis use disorder, increasing their engagement in multiple treatment modalities and reducing stigma-based shame. They bring their visiting parent to a joint visit and ask that you review this model with them.

1. What neuroanatomical regions are associated with each stage of the addiction cycle?
   A. Binge intoxication, striatum; withdrawal, extended amygdala; craving, prefrontal cortex
   B. Binge intoxication, striatum; withdrawal, prefrontal cortex; craving, extended amygdala
   C. Binge intoxication, extended amygdala; withdrawal, prefrontal cortex; craving, striatum

D. Binge intoxication, striatum; withdrawal, extended amygdala; craving, habenula
E. Binge intoxication, prefrontal cortex; withdrawal, extended amygdala; craving, habenula

Answer: A

Explanation: Binge intoxication, striatum; withdrawal, extended amygdala; craving, prefrontal cortex. The striatum is composed of the caudate and putamen; the ventromedial striatum includes the nucleus accumbens (NAc), which mediates the rewarding effects of intoxication in addiction. The homeostatic anti-reward system drives the withdrawal/negative affect stage of the addiction cycle; it involves the central division of the extended amygdala, a circuit composed of the amygdala's central nucleus, bed nucleus of the stria terminalis, and a transition zone in the NAc shell, as well as the habenula. The craving stage is marked by conditioned stimulus-induced release of dopamine in the NAc, motivating compulsive drug-seeking behavior; the prefrontal cortex's executive function manages this cue-induced impulse using two opposing systems, termed the Go system (which engages automatic habitual behavior) and Stop system (which inhibits these habitual behaviors). Prefrontal glutamatergic projections from these systems to the VTA and striatum modulate the response to craving. In addition, the Stop system is hypofunctional, and the Go system is hyperactive alongside a sensitized anti-reward system.

2. Ongoing neurodevelopment in adolescence (which extends into the third decade of life) allows for more rapid neuroadaptation to psychotropic substance use and development of SUD. Uneven development across different circuits also affects the propensity to initiate substance use; what circuits are underdeveloped in this period?
A. Limbic affective system
B. Pyramidal motor system
C. Extrapyramidal striatal system
D. Default mode network system
E. Prefrontal cognitive control system

Answer: E

Explanation: Prefrontal (top-down) cognitive control system is underdeveloped relative to the striatal and limbic systems, the latter two motivating impulsive, reward-seeking behavior and greater affective reactivity. This imbalance increases risk of substance use during a sensitive period of neurodevelopment.

References

1. Substance Abuse and Mental Health Services Administration (SAMHSA). Key substance use and mental health indicators in the United States: results from the 2017 National Survey on Drug Use and Health (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. 2018. Retrieved from https://www.samhsa.gov/data/.

2. Koob GF, Arends MA, Le Moal M. Drugs, addiction, and the brain. Waltham, MA: Academic Press (Elsevier); 2014.
3. Crum RM. Chapter 2: The epidemiology of substance use disorders. In: Ries RK, Fiellin DA, Shannon C, Miller RS, editors. The ASAM principles of addiction medicine. 5th ed: Wolters Kluwer; 2014.
4. Grant BF, Goldstein RB, Saha TD, et al. Epidemiology of *DSM-5* alcohol use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA Psychiat. 2015;72(8):757–66. https://doi.org/10.1001/jamapsychiatry.2015.0584.
5. American Society of Addiction Medicine (ASAM). Terminology related to the spectrum of unhealthy substance use. ASAM Board of Directors; July 2013. Retrieved from https://www.asam.org/docs/default-source/public-policy-statements/1-terminology-spectrum-sud-7-13.pdf?sfvrsn=2.
6. National Institute on Drug Abuse. Substance use in women: sex and gender differences in substance use. National Institutes of Health; July 2018. Retrieved from https://www.drugabuse.gov/publications/research-reports/substance-use-in-women/sex-gender-differences-in-substance-use.
7. Substance Abuse and Mental Health Services Administration (SAMHSA). 2016 NSDUH: race and ethnicity summary sheets; 2016. Retrieved from https://www.samhsa.gov/data/report/2016-nsduh-race-and-ethnicity-summary-sheets.
8. Breslau J, Aguilar-Gaxiola S, Borges G, Kendler KS, Su M, Kessler RC. Risk for psychiatric disorder among immigrants and their US-born descendants: evidence from the National Comorbidity Survey Replication. J Nerv Ment Dis. 2007;195(3):189–95.
9. Zhang X, Martinez-Donate AP, Nobles J, Hovell MF, Gudelia Rangel M, Rhoads NM. Substance use across different phases of the migration process: a survey of Mexican migrants flows. J Immigr Minor Health. 2015;17(6):1746–57.
10. Rehm J, Room R. The cultural aspect How to measure and interpret epidemiological data on alcohol-use disorders across cultures. Nordic Stud Alcohol Drugs. 2017;34(4):330–41.
11. Wilens TE. Attention deficit hyperactivity disorder and substance use disorders. Am J Psychiatry. 2006;163:2059–63.
12. Volkow ND. Substance use disorders in schizophrenia--clinical implications of comorbidity. Schizophr Bull. 2009;35(3):469–72.
13. Centers for Disease Control and Prevention. HIV Surveillance Report, 2016; vol. 28. http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published November 2017. Accessed Oct 27, 2018.
14. Zibbell JE, Asher AK, Patel RC, Kupronis B, Iqbal K, Ward JW, Holtzman D. Increases in acute hepatitis C virus infection related to a growing opioid epidemic and associated injection drug use, United States, 2004 to 2014. Am J Public Health. 2018;108(2):175–81.
15. Forray A. Substance use during pregnancy. F1000Res. 2016;5:F1000 Faculty Rev-887.
16. Volkow ND, Boyle M. Neuroscience of addiction: relevance to prevention and treatment. Am J Psychiatry. 2018;175(8):729–40.
17. National Institute on Drug Abuse. Overdose death rates. National Institutes of Health; Aug 2018. Retrieved from https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates.
18. Substance Abuse and Mental Health Services Administration. Drug Abuse Warning Network (DAWN), 2011: National Estimates of Drug-Related Emergency Department Visits. HHS Publication No. (SMA) 13-4760, DAWN Series D-39. Rockville, MD; 2013.
19. Gelernter J, Kranzler HR. Genetics of Addiction. In: Galanter M, Kleber HD, Brady KT, editors. The American Psychiatric Publishing Textbook of Substance Abuse Treatment. 5th ed; 2015. Accessed Oct 27, 2018 via https://psychiatryonline-org.ezproxy.med.cornell.edu/doi/full/10.1176/appi.books.9781615370030.mg02.
20. Prom-Wormleya EC, Ebejerb J, Dickc DM, Bowers MS. The genetic epidemiology of substance use disorder: a review. Drug Alcohol Depend. 2017;180:241–59.

21. Anton RF, Oroszi G, O'Malley S, et al. An evaluation of μ-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. Arch Gen Psychiatry. 2008;65(2):135–44.
22. Uhl GR, Liu Q, Drgon T, et al. Molecular genetics of successful smoking cessation convergent genome-wide association study results. Arch Gen Psychiatry. 2008;65(6):683–93.
23. Ahmad T, Valentovic MA, Rankin GO. Effects of cytochrome P450 single nucleotide polymorphisms on methadone metabolism and pharmacodynamics. Biochem Pharmacol. 2018;153:196–204.

Screening, Evaluation, and Diagnosis of Substance Use Disorder

4

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High-Yield Review Points

- Positive screenings for SUD should facilitate a more comprehensive assessment that contributes to diagnostic impressions and yields clinically useful information for treatment planning.
- Based on the DSM-5, an SUD is determined based on meeting at least 2 of 11 criteria within the same 12-month period, which incorporate some aspects of the old DSM-IV categories of abuse and dependence (except legal problems), as well a new one (experience of substance cravings) into a single disorder with three levels of severity (mild, moderate, and severe).
- A comprehensive clinical diagnostic evaluation for SUD should start with a thorough history of presenting illness, followed by a systematic assessment of past and present substance use history, other psychiatric history, family history, social and developmental history, and a psychiatric/mental status exam.
- Most individuals will experience recovery of cognitive and motor functions after an extended period of sobriety, but recovery of specific cognitive functions occurs at different rates and is impacted by many factors including age, polysubstance use, duration, and severity of substance use [1].

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Screening

Screening tests for SUD are relatively brief measures that are designed to identify someone who may be at risk for alcohol- or substance-related disorders, and who may be offered or referred for further evaluation and treatment. Screening measures are not intended to yield a diagnosis or a comprehensive account of alcohol or substance use history. Positive screenings for SUD should facilitate a more comprehensive assessment that contributes to diagnostic impressions and yields clinically useful information for treatment. In general, structured or semi-structured interviews can collect more comprehensive, detailed information relative to informal interviews while reducing variability from interviewer differences [2]. Structured interviews are fully scripted, requiring strict adherence to questions and allowing a limited range of responses with no individualized follow-up. Semi-structured interviews also utilize a scripted format but allow for clinical judgment in the use of queries to elicit more detailed information from the respondent. Both interview types lend themselves to psychometric consideration because of their standardized administration and rigorous approach to identifying specific diagnostic criteria (typically DSM or ICD elements).

Screening measures can be selected according to how well they perform in specific target populations (adults vs adolescents, psychiatric inpatients, veterans, etc.) or particular environments (primary care clinics, counseling centers, online computerized screening). Many screening measures are self-administered (paper/pencil or computer) and require a minimum expenditure of time. Optimal brief screening has been investigated using only a few specific questions derived from larger screening measures. Statistically, screening measures are evaluated in terms of their ability to correctly identify true positives (sensitivity) or true negatives (specificity). The selection of a test based on sensitivity or specificity values usually depends on the significance (in terms of cost or severity of an outcome) of an incorrect result in either condition.

Adequate screening properties have been achieved with only two questions culled from longer screening tools (87.2% sensitivity, 79.8% specificity) [3]. Generally, a positive response from a two- or three-question screen would be followed by a more comprehensive screening test. Patient self-reported information about substance use is typically "pre-screened" through the use of brief, focused questions, such as the National Institute on Alcohol Abuse and Alcoholism's (NIAAA) 3 Question Screen or the National Institute on Drug Abuse's (NIDA) Quick Screen.

Here is a summary of brief, initial screens for substance use:

AlcoholScreening.org, managed by Join Together, is a free patient self-assessment tool that helps identify if a person is endorsing alcohol consumption that may be harmful to their health.

The CAGE Questionnaire, developed by Bowles Center for Alcohol Studies Founding Director Dr. John Ewing, is a four-item questionnaire that can indicate

potential problems with alcohol [4]. (CAGE AID was adapted to include drugs.) It usually only takes 5 minutes to administer and can be used in any medical clinic. "CAGE" is an acronym formed from the italicized letters in the questionnaire (cut-annoyed-guilty-eye):

- Have you ever felt you should *C*ut down on your drinking?
- Have people *A*nnoyed you by criticizing your drinking?
- Have you ever felt bad or *G*uilty about your drinking?
- Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (*E*ye opener)?

Scoring: Item responses on the CAGE are scored 0 or 1, with a higher score an indication of alcohol problems. A total score of 2 or greater is considered clinically significant.

The CRAFFT screening interview is series of six questions screening instrument designed for children under the age of 21 to identify if they have potential problems with alcohol and other drug use disorders.

Part A includes questions about the use of alcohol, marijuana or hashish, and other substances used to get high (illegal drugs, over the counter and prescription drugs, or anything used as an inhalant) during the past 12 months. Part B assesses context of use (drinking with others or alone, reason for use), including hazardous conditions (driving or being driven by someone that is high, gotten in trouble while using, or forgetting actions one did while using) and interpersonal functioning (family or friends asking you to cut down).

Scoring: Two-part questionnaire – if the patient answers yes to any of the first three questions, the patient will be asked a set of six questions that correspond to each letter in the name. Each yes answer gets a score of 1, and then after all questions have been answered, a total cumulative score is given. The higher the score, the greater the predictive value of future drug abuse and therefore the need to refer the patient for a full assessment by an addiction provider.

NIAAA 3 Question Screen is developed by NIAAA to assess problematic alcohol use [5].

1. How many days per week do you drink alcohol?
2. On a typical day when you drink, how many drinks do you have?
3. What is the maximum number of drinks you had on any given day in the past month?

Scoring: The NIAAA guidelines for maximum drinking limits for healthy men up to age 65 are no more than 4 drinks in a day and no more than 14 drinks in a week. For healthy women (and healthy men over age 65), the guideline is no more than 3 drinks in a day and no more than 7 drinks in a week.

ASSIST is the **A**lcohol, **S**moking, and **S**ubstance **I**nvolvement **S**creening **T**est [6]. It is a brief screening questionnaire developed by the World Health Organization (WHO). It collects information about lifetime and past 3-month use and dependence, associated problems, risk of current or future harms, and injecting drug use. This screener contains 7 questions about each of 10 substance and 1 question about IV drug use.

Scoring: Provides feedback about each the level of risk to the patient with continued use (low = 0–3, moderate = 4–26 or high = 27+) with cumulative score for each substance, with the only exception for alcohol where low = 0–10 and moderate = 11–26, high = 27+.

AUDIT is the **A**lcohol **U**se **D**isorders **I**dentification **T**est (AUDIT) is a 10-item screening instrument, developed by the World Health Organization (WHO), to identify excessive and harmful patterns of alcohol use [7].

Scoring: The 10 AUDIT questions are scored with options responses scaled 0–4, where 0 indicates "never" to 4 is "daily or almost daily." A score of 8 or more is associated with harmful or hazardous drinking, a score of 13 or more in women, and 15 or more in men, is likely to indicate alcohol dependence.

Michigan Alcoholism Screening Test (MAST) is a 28-item screen designed to assess problems with alcohol use [8].

Scoring: Add up the points for every question you answered with YES, for Q23 and Q24 multiply the number of times by points: score of 0–3, no apparent problem; score of 4, early or middle problem drinker; and score of 5 or more, problem drinker (alcoholic).

The Drug Abuse Screening Test (DAST) is a 28-item self-reported scale, developed by Harvey Skinner of the Toronto Center for Mental Health [9], which consists of items similar to the Michigan Alcoholism Screening Test (MAST). This scale does not screen for alcohol/tobacco. DAST assesses a pattern of use behavior for last 12 months prior to administration.

Scoring: All questions are answered on a yes or no basis with a scoring of 1 point for every yes answer. Cumulative score of all answers is used to rate the degree of intensity of the drug use problem and is used to direct the recommended type of intervention. Scoring is as follows: score of 1–2, possible low level of drug use (it is recommended that the patient be reassessed in the future for worsening of drug problems); score of 3–5, possible moderate drug use problem; score of 6–8, possible substantial drug use problem; and score of 9–10, significant drug use problem.

The Wisconsin Initiative to Promote Healthy Lifestyles' (WIPHL) Sample Behavioral Health Screen collects information about patients' drug and alcohol use and screens for depression and exposure to domestic violence.

Standardized, Psychometric Tests for Substance Use Disorders (SUD)

An array of evidence-based psychometric tests exists for screening and assessment of SUD. The primary rationale for adding psychometric tests to clinical interviews is to increase the overall diagnostic accuracy and predictive validity of the assessment process. Informal, unstructured clinical interviews are ubiquitous in SUD assessment process. In addition to basic information gathering, the unstructured interview can foster rapport building, provide psychoeducation about treatment options, and affords the flexibility for dealing with clinical emergencies. But clinicians using unstructured interviews typically overestimate their diagnostic accuracy: increased error variance from interviewer effects (sociodemographic variables) is more likely to occur when assessing sensitive information like substance use. A multi-method assessment approach that combines a clinical interview with psychometric tests and additional sources of information (medical records, collateral information, biological tests) can improve accuracy of diagnosis, augment patient characterization, and enhance prediction of treatment outcomes [10].

Psychometric tests and interviews for SUD can be broadly classified according to the purpose and phase (timing) of the assessment. Brief screening measures are used to identify those at-risk for these disorders from a larger cohort; structured interviews or self-report instruments provide information for a formal diagnosis based on specific SUD criteria; and comprehensive mental health assessments identify comorbid disorders and help to provide additional diagnostic information for treatment planning. Within these categories, considerations for test selection include choices about (a) clinician-administered measure versus self-report, (b) manual scoring versus computer-assisted scoring, (c) current or recent alcohol/drug use versus lifetime/chronic use, (d) clinical versus research application, and (e) target populations: non-specific groups versus subgroups with characteristics of interest (age, gender, ethnicity, or race).

Statistical and Psychometric Information for Test Selection

Selection of an appropriate, evidence-based test involves both theoretical and pragmatic considerations. In the most general sense, reliability refers to the accuracy of measurement and sources of error when a test is administered across time, over different settings, and by different administrators. Estimates of test-retest reliability indicate how consistently the test evaluates a given person or group over multiple occasions (i.e., temporal stability). This measure can vary with the how stable or transient a given trait or characteristic might be over a given length of time. Estimates of inter-rater reliability indicate the degree of measurement error attributable to differences between examiners or styles of administration. Internal consistency measures estimating how well the items within a given scale or test correlate with each other. The uniformity of the test content can also be assessed with split-half

reliability measures (comparing half of the test items with the remaining half) to determine the extent to which individual test items are accurately measuring the construct of interest.

Validity is an indicator of how well a test actually samples or measures the characteristic of interest—determining if the test is accurately assessing the condition or trait that it proposes to measure. Within this category, test validity can be evaluated by comparing results to some outside performance measure. Criterion validity can indicate how well a test measures a specific outcome at the present time (concurrent validity) or at some point in the future (predictive validity). Content validity refers to how well items within a test accurately sample the characteristic, disorder, or domain of interest. Construct validity is established over time as the test is compared with both related and dissimilar characteristics and tests. Construct validity evolves with accrued research on the test, comparing and contrasting it with other constructs. Finally, incremental validity reflects to what extent the test results yield information over and above what is to be gained through other methods. For example, does adding a self-report measure improve diagnostic accuracy over an interview alone?

Psychometric Assessment

The classification of patients through structured interviews is considered the "gold standard" when comparing predictive validity of other tests. Disadvantages can include lengthy administration time and training time required for correct administration. Frequently used structured and semi-structured interviews include Addiction Severity Index (ASI), Composite International Diagnostic Interview (CIDI), Structured Clinical Interview for DSM-IV/DSM-5 (SCID), Alcohol Use Disorders and Associated Disabilities Interview Schedule (AUDADIS-5), Psychiatric Research Interview for Substance and Mental Disorders (PRISM), and Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA). It should be noted that the transition to DSM-5 signaled a shift from a largely categorical diagnostic approach to a combination categorical and dimensional approach. Previous categories of abuse and dependence are combined into a single disorder for alcohol or substance use in DSM-5 that is measured on a continuum from mild to severe. Consequently, diagnostic tests should be reviewed to confirm which criteria are used (DSM-5, ICD10).

Psychiatric comorbidity is associated with worse health outcomes, more complex clinical management, and increased health care costs [11]. When a co-occurring disorder has been detected, a comprehensive assessment can help distinguish the relative severity of each disorder and identify the functional consequences of comorbidity. Psychiatric comorbidity can complicate treatment and have an adverse effect on the outcome of substance use disorders. Psychodiagnostic inventories can be a useful addition to the SUD assessment process, clarifying diagnoses with similar symptoms and identifying associated risk factors. However, such testing is time-intensive for both administration and interpretation, with high levels of training and

expertise required. These inventories can provide information about acute clinical syndromes, personality styles/disorders, interpersonal relationships, and specific high-risk behaviors that are relevant for both diagnosis and treatment of SUD. The most frequently used instruments are discussed below.

MMPI2/ MMPI2RF: The Minnesota Multiphasic Personality Inventory (version 2, or Revised Format) [12] is a 567-item true/false response inventory that yields dozens of variables pertaining to current mental health disorders, and a host of variables describing specific behaviors, and clinical syndromes. It is the most frequently used and cited psychological assessment inventory in use at this time, with a wealth of prior research that has yielded specific indices pertaining to individuals with alcohol or substance use disorders. The MMPI2 includes four specific scales that assess alcohol/drug abuse. The Addiction Admission Scale and Substance Abuse Scale are direct measures of substance use and its consequences. The MacAndrew Alcoholism (rev) Scale and the Addiction Potential Scale evaluate abuse indirectly through endorsement of behaviors or situations highly correlated with substance use disorders. There are also two sets of specific "critical items" that are flagged by the MMPI2 to identify potential alcohol/drug use.

MCMI3/4: The Millon Clinical Multiaxial Inventory (versions 3, 4) is a 195-item true/false inventory that emphasizes long-standing, characterological traits and identifies possible maladaptive personality styles and disorders [13]. This test may be useful in that it provides scales for specific personality disorders that have often been associated with increased risk for alcohol or drug use. It also measures acute clinical syndromes (Alcohol and Drug Use Scales) in terms of base rates to identify the presence or prominence of key behaviors and symptoms.

PAI: The Personality Assessment Inventory [14] is a 344-item inventory using a 4 point Likert response scale to identify psychopathology and personality styles, and treatment variables. This inventory offers two individual scales that quantify alcohol problems based on problems with excessive intake, and a second scale of drug problems indicating probable excessive recreational drug use. These personality inventories can help to identify additional areas of clinical concerns in individuals with SUD and adds information valuable for treatment planning.

Comorbidity can also extend to cognitive dysfunction in SUD. The neurotoxic effects of alcohol and many recreational drugs can have both acute and long-term effects on brain functioning, contributing to mild or major neurocognitive disorders over time. It is not uncommon for an assessment of functional status in SUD to suggest evidence of possible cognitive dysfunction. There are brief cognitive screening measures available that are sensitive (but not specific) for cognitive impairment, and these can prove useful for initial assessments. These include Mini Mental State Exam (MMSE), Montreal Cognitive Assessment (MoCA), and St. Louis Mental Status Exam. However, these cognitive screening tests should not be administered during acute intoxication, nor should they be used until an individual is medically stable after withdrawal from alcohol or drugs. Cognitive impairment is usually the

most severe in the first few weeks of abstinence [1]. If subsequent cognitive screening suggests ongoing impairment, a full neuropsychological assessment is recommended to evaluate all cognitive domains. This comprehensive test battery is not administered in the first few weeks of sobriety because variable attention and information processing deficits can negatively impact overall performance. Most individuals will experience recovery of cognitive and motor functions after an extended period of sobriety, but recovery of specific cognitive functions occurs at different rates and is impacted by many factors including age, polysubstance use, duration, and severity of substance use [1].

Evaluation and Diagnosis

What Is an SUD and What It is Not?

While substance use refers to merely using a particular substance in any amount, it is generally thought of as an appropriate level of use, which doesn't necessarily involve excessive or risky level of use, or any dependence or addictive behavior. Moreover, "at-risk" use refers to a level of use which may be higher than typical use rates in the population and may place someone in a category of individuals at a higher risk of developing an SUD. Similarly, "problem use" or "hazardous use" typically refers to a level of use that may have put someone's health at risk (e.g., consuming the substance in context that make it dangerous, such as driving or operating heavy machinery) or have interfered with their financial or social functioning. However, it may not necessarily qualify for an SUD, particularly if this type of use has happened on an occasional or specific basis (e.g., in response to a stressor) and does not happen chronically.

In contrast, based on the DSM-5, an SUD is determined based on meeting at least 2 of 11 criteria within the same 12-month period, which incorporate some aspects of the old DSM-5 categories of abuse and dependence (except legal problems), as well a new one (experience of substance cravings) into a single disorder with three levels of severity (mild, moderate, and severe). This new scheme provides an overarching structure of 11 general criteria applicable to any substance being considered, with the possibility to diagnose a separate substance-specific SUD (e.g., alcohol use disorder, opioid use disorder). These criteria include:

1. The drug is often taken in a larger amount or over longer period than intended.
2. Persistent desire or unsuccessful attempts to cut down.
3. A great deal of time is spent in activities to acquire, use, or recover from the drug.
4. Experience of cravings/urges.
5. Recurrent drug use resulting in failure to fulfill major obligations (e.g., work, home).
6. Continued drug use despite persistent interpersonal problems caused by the drug.

7. Important social, occupational, or recreational activities are given up/reduced because of drug use.
8. Recurrent drug use in situations in which it is physically hazardous.
9. Continued use of the substance despite knowledge of persistent problems caused by it.
10. Tolerance (i.e., need for markedly increased amounts of drug to achieve intoxications/desired effect, or markedly diminished effect with continued use of same amount).
11. Withdrawal (i.e., drug-specific symptoms, or the substance, or closely similar substance, is taken to relieve or avoid withdrawal symptoms).

In terms of severity, individuals who meet two to three of these criteria qualify for a mild SUD, meeting four to six criteria indicate a moderate SUD, and meeting seven or more criteria would indicate a severe SUD diagnosis.

Not an SUD Firstly, legal problems related to the substance use, a previously recognized abuse and dependence criteria from DSM-5, have been removed from consideration in an SUD diagnosis as this criterion was found to be culturally biased and not reliable across cultures and settings [15]. Having current or past problems with the law may reflect a pattern of substance dealing or criminal activity rather than a personal addictive profile. That being said, parts of a history, such as a charge for driving under the influence (DUI) is still critically relevant to a potential SUD diagnosis as it may pertain to several SUD criterion, including tolerance and underestimation of substances effect on cognition, recurrent use in hazardous conditions, and problems fulfilling major role obligations. Secondly, recent ingestion of a substance resulting in diagnosis of intoxication does not necessarily reflect a pattern of addictive behavior and a diagnosis of SUD. Intoxication could relate to a one-time experimentation with a particular substance, or even exposure to a prescribed substance (e.g., opioid medication), and an individual with such presentation should not be diagnosed with an SUD unless they meet at least two of the SUD criteria in the same 12-month period. Finally, substance-induced withdrawal, which presents with drug-specific physiological and psychiatric symptoms resulting from recent cessation or reduction of a substance, does not in itself constitute an SUD diagnosis, unless a more prevalent pattern of use and associated SUD criterion would also be met. That is, while withdrawal symptoms may result from stopping use, which was previously heavy or prolonged, such pattern of use should be specially assessed for SUD criteria to determine whether an SUD diagnosis is warranted.

Substance Use Evaluation

To accurately and effectively assess for substance use pathology, several broad assessment areas should be considered, in order to not only make an accurate SUD diagnosis but to determine potential co-occurring mental and physical illness, the individual's protective and risk factors, and the individual's goals and specific

situation. This information will ultimately help to develop an individualized treatment plan. The goal is to obtain a broader picture of the context and long-term behavioral history in which present symptoms are occurring, including potential past SUD diagnoses, recovery and relapse history, co-occurring disorders, personality features, as well as socio-economic, developmental, and interpersonal factors.

History of Presenting Illness (HPI): This part of the assessment is concerned with gathering information on current symptoms and precipitating factors, including substance use and other psychiatric and medical pathology. This is the most open-ended component of the assessment, in order to collect both factual details on the current clinical symptoms, but also the subjective perspective and experience of those symptoms as described by the patient. Thus, while it is not necessary at this stage to systematically check for use of all substances, a thorough assessment of level of use and review of SUD criteria should be conducted for each substance mentioned by the patient as currently being used.

Recognizing that an accurate self-assessment of how much substance is consumed is unlikely in most patients; one should provide specific, concrete cues to gage how much is used and how often. Evaluating quantity with objective units (e.g., grams of alcohol) is ideal, but not necessarily feasible if the patient is not familiar with those standards. Many patients will report opioid use in terms of number of bags or bundles (10 bags) use, but determining the potency or composition (heroin, fentanyl, morphine, etc.) is difficult and varies considerably. Cocaine is sometimes reported in terms of grams or the cost (e.g., $20 per day). Marijuana is often reported in ounces, but newer waxes, edibles, and other forms are often reported based on (often unverified) percentage Tetrahydrocannabinol (THC) or cannabidiol (CBD). In regard to alcohol, “one drink” is relatively vague and subjective measure, which is unlikely to align with current serving size recommendations. For instance, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) provides differential drinking benchmarks for men and women, which keeps them at low-risk for developing an AUD: no more than 4 drinks per occasion and no more than 14 drinks per week for men, and no more than 3 drinks per occasion and no more than 7 drinks per week for women. However, in this definition, a drink is defined as 12 ounces of regular 5% alcohol beer, 5 ounces of wine (1–21% alcohol), or 1.5 ounces of 40% alcohol distilled spirits [16]. Typically, one drink as perceived and endorsed by a patient will represent a larger quantity (e.g., a regular bottle of strong 8% beer, or large ounces can of regular beer). The speed of drinking within a particular day and the frequency of such drinking sessions will also be critical to estimate, as it could reveal a binging tendency even within current daily amounts [16].

Once level of use has been evaluated, even if within a low-risk category, the presences of potential SUD symptoms still needs to be assessed. One may experience significant cravings and related ruminations and functional impairment even if objectively using within what is considered low to moderate use. To understand the context of use, consider potential precipitating events that may have triggered the

current illness. Did the patient experience a recent loss or breakup? Are there any interpersonal conflict(s) with those close to them? Has there been any recent failures or significant delays at school or work, or a recent loss of employment?

Mood and anxiety symptoms will be common co-occurring conditions to evaluate (see other psychiatric history section below). The timeline of those symptoms with respect to the substance use, i.e., whether one of symptoms was a triggering factor for the substance use or vice versa, will help with diagnosis of a primary substance use disorder versus a substance-induced psychiatric disorder. For instance, has depression, anxiety, and/or manic symptoms onset occurred first, leading to substance use? Or, has substance use onset/relapse preceded the development of the affective symptoms? Do they always/only co-occur together. If available, results from screening questionnaires and mood scales may help to guide the patient to identify and verbalize the most salient struggle and maladaptive pattern (i.e., chief complaint), but also to consider all potential ongoing symptoms and difficulties. These can also help refocus the interview while minimizing risk of omission of important data on the patient's part. With consent from the patient, it will be particularly useful to talk to collateral informants (e.g., spouse, close relatives, friends), who may provide more objective or complementary data on the patient's history, current symptoms, and level of functioning. Beware of bias on the part of the informant.

Substance Use and Treatment History: This goal is to get a thorough, long-term picture of the patient's pattern of use for all main substance types, thus reviewing some substances that may not have been reviewed thoroughly during the HPI. Substances that should be systematically considered are the most commonly used based on the geography, availability of drugs, demographics of the patient, and other factors. Common substances needing evaluation include alcohol, cannabis, tobacco, caffeine, methamphetamine/amphetamine, cocaine, benzodiazepines, opioids, and other substances such as hallucinogens (e.g., lysergic acid diethylamide (LSD), mushrooms containing psilocybin), 3,4-methylenedioxy-methamphetamine (MDMA; ecstasy), phencyclidine (PCP; angel dust), inhalants, etc. Importantly, both prescription and illicit forms of the substance should be considered. For instance, maladaptive use of stimulants could involve prescription methylphenidate (prescribed to patient or obtained elsewhere) or the illicit methamphetamine. Prescription opioid and benzodiazepine medications used to treat pain, sleep, and anxiety are associated with significant addictive side effects and may be more commonly encountered than heroin in certain regions or populations.

For each substance endorsed by the patient, the first step should be to determine the general chronology and level of maladaptive use over time. The provider should inquire about the following: name of substance used, when use first started, length of time used, frequency and pattern of use with special emphasis on use during the past week, date and time of last use, route of administration, amount, cost, and purpose (e.g., to get high, to avoid withdrawal, to relieve depression, to sleep, or to relieve side effects of other drugs). Focus on key periods of use with relapse triggering event(s) and subsequent typical pattern of use (i.e., how much, how

often), and phases of recovery should be assessed. Questions about the impact of the substance on a person can be asked, as well as specific DSM-5 SUD criteria. Substance-specific questions are helpful. For example, one may ask about overdoses with opioids or benzodiazepines; about black outs, seizures, or delirium tremens with alcohol; and about cardiac side effects with stimulants. For drugs previously used, ask the following: age at which drug use started, length of time used, and adverse effects. For previous treatment experiences inquire about where, what kind, and the outcome. For prescription drugs currently used inquire about the following: name, reason for use, amount, frequency, duration of use, and last dose. State prescription drug monitoring programs (PDMP) should be utilized when available.

To accurately estimate overall severity, maladaptive use, and relapse cycle, it is important to identify and prioritize a detailed assessment of the period of heaviest use, in terms of level and pattern of use and specific physiological and psychosocial SUD criteria. Also, for most of these substances, keep in mind each drug may be consumed in one or multiple forms (ingested, chewed, smoked, snorted/inhaled, injected in blood stream, etc.). In addition, the presence of medical or other physiological consequences of use (e.g., withdrawal, intoxication symptoms, blackouts) will be key factors in determining severity of use and whether some criteria are (e.g., withdrawal, tolerance) present. One should assess all criteria for every endorsed substance (or confirm any previously revealed criterion symptom during the HPI) and get a sense of how many of these criteria were met at different periods of use in the patient's past history (starting at the age of first use to present).

Based on how many of the symptom criteria are being met for a particular substance, a diagnosis of SUD and its severity level can be determined, with two to three being mild, four to five being moderate, and six or more criteria met being considered severe SUD.

Substance use history also includes periods of recovery and remission. According to the Substance Abuse and Mental Health Services Administration (SAMHSA) [17], this is a multi-domain *process of change* which should be assessed in terms of health, home/shelter purpose (e.g., professional endeavors), and community (i.e., relationships, social networks). Thus, when assessing substance use and treatment history, it is important to recognize that recovery may not necessarily include full abstinence from the problem substance(s) and that recovery happens on a continuum, which may involve non-problematic use. According to DSM-5, a period of remission is defined as not meeting any of the SUD diagnostic criteria besides cravings (patient may experience cravings) and can be classified into "early remission" if this is met for at least 3 months, or "sustained remission" if met for at least 1 year [15]. Inquiring about the patient's past ability to initiate and sustain recovery will provide a way to understand the specific protective and risk factors that may foster the patient's successful recovery or impede it.

Other Psychiatric History: Given the high rate of co-occurring disorders among individuals with substance use problems, it will be particularly important to get a full psychiatric history and the potential relationship between comorbid disorders and substance use to better inform treatment planning. Mood disorders, including

depression and bipolar disorder, and anxiety disorders are the most common psychiatric comorbidities among individuals with SUDs [18]. A comprehensive psychiatric history will thus be essential to disentangle potential comorbidities that may warrant a more integrated intensive treatment planning after assessment. Such assessment should include any history of self-injurious behavior and suicide attempt (including the extent to which those potential attempts were planned and to what extent the patient sought help), tendency for violence, any known past diagnosis of mental illness, any history of traumatic events (including sexual, verbal, physical abuse), any prior hospitalizations and/or inpatient treatment for psychiatric reasons, any prior experience with psychotherapy and/or other behavioral treatment (and if so how often, for how long, and with what results), and any prior use of psychotropic medications (including dosage and observed effectiveness).

Family History: A family history of psychiatric illness, particularly SUD, is well-recognized risk factor for developing an SUD [19], which may help to corroborate a patient's diagnosis and also shed light on their potential disposition for recovery and treatment response. In addition, such background can shed light and help focus assessment of social and developmental history, e.g., if parents or close relatives were abusive, neglectful, absent while in treatment, etc. Note which relative exhibited which disorder to provide information on how closely related, but also to evaluate potential exposure to emotionally taxing and/or abusive behavior, and potential modeling of maladaptive patterns.

Social/Developmental History: Collecting social history can not only provide the assessor with sense of the patient's socio-economic background, education, and financial stability, but it can be a critical aspect of assessing for history of trauma within the family they grew up with, and the development of early psychiatric pathology in this context. More recent social history can also provide important information about current risk factors for substance abuse and maintenance of addiction, e.g., romantic partner or close friend who is using, living environment that facilitates access to substance, and exposure to violence/abuse. Importantly, it can shed light on how substance use is affecting the patient's current level of functioning from a social, professional, and financial perspective, which may not have been fully captured during the HPI. Likewise, this portion of the assessment can help identify activities, hobbies, and types of relationships, friendships that are or have been nourishing and protective to the patient in the past, which can be incorporated in treatment planning.

Medical History: A medical history assessment should survey for any allergies, current medications and their indications, and any relevant medical conditions that may be related to or commonly co-occur with substance use, could be relevant for medication treatment, or could affect their health, functioning, and treatment. Common assessments include the presence of any head injury, seizures, neurocognitive impairment, coronary artery disease and arrhythmias, pulmonary problems, thyroid problems, anemia, serious abdominal problems (pancreatitis,

liver disease, kidney failure, hepatitis C), and sexually transmitted or other infections (e.g., HIV). Such conditions and current medication regimen will be particularly relevant to plan recovery and substance use discontinuation in a safe manner for the patient. Diseases commonly associated with drug use, particularly among users of opioids by injection, are viral (e.g., HIV, Hepatitis C) and bacterial infections. Other diseases such as sexually transmitted diseases, syphilis, and tuberculosis also have a higher prevalence among people with substance use.

Psychiatric/Mental Status Exam: A mental status exam should include patient's attitude and behavior (e.g., cooperative vs guardedness), speech quality, presence of psychomotor retardation or agitation, mood and affect, thought process and content (e.g., linear; goal-directed; associations, psychotic content), perceptual disturbances, suicidal ideation, homicidal ideation, orientation to person/place/time, and attention and concentration. In addition, observance of appearance and grooming, gait and station, presence of tremors, or abnormal movements should be noted.

Review Questions

1. Henry just got off from work and pours himself a glass of beer. His partner arrives and asks him if he would like to join him for another drink. Henry responds "I think I should really just have one tonight." When dessert arrives, he thinks it may not do any harm to have his usual glass of moscato, though he feels conflicted about it. He eventually gives in thinking "it won't make much a difference if I have a glass or two." What does Henry's initial response exhibit based on the screening criteria in the CAGE screener?
   A. The individual has felt he/she should **C**ut down on their drinking.
   B. The individual feels a loss of **C**ontrol on their drinking.
   C. The individual has noticed increased **C**riticism from closed ones for their drinking.
   D. The individual has been **C**aught drinking on the job.
   E. The individual has **C**onsumed an alcoholic drink first thing in the morning to steady their nerves or to get rid of a hangover.

   Answer: A. Henry's behavior is indicative of the criteria of feeling he should "**C**ut down" on his consumption of alcohol, corresponding to the "C" in the CAGE questionnaire. The other "C" responses are not a criterion in the CAGE screener.
2. Betty is a 65-year-old, Caucasian female, divorced, with a past medical history of high blood pressure, gout, diabetes, and complaints of depression since age 40 after her divorce. She started drinking alcohol at age 40 after her divorce, about 3 bottles per wine per week at the peak. She currently has up to 2 drinks per day, but less than 5 total drinks in a week. What standard is Betty currently following that is in accordance to NIAAA Guidelines?

A. Betty is following the guideline that for healthy women no more than 3 drinks in a day.
B. Betty is following the guideline that for healthy women under age 65 no more than 10 drinks in a week.
C. Betty is following the guideline that for healthy women no more than 4 drinks in a day.
D. Betty is following the guideline that for healthy women no more than 8 drinks in a week.
E. For all individuals, the guideline is that you can have more than 4 drinks in a day if they consume only beer, but only 3 drinks per day if they consume only hard liquor.

Answer: A. The NIAAA guidelines for low risk drinking in healthy men up to age 65 are: no more than 4 drinks in a day and no more than 14 drinks in a week. For healthy women (and healthy men over age 65), the guideline is no more than 3 drinks in a day AND no more than 7 drinks in a week.

3. Mike is 22 years old and working on his Bachelor degree in computer science. While he is on track in terms of his grades, he is definitely enjoying the "college life" and regularly goes to parties where he has more than a few drinks. He has also been developing a taste for smoking marijuana, which he feels helps him focus during the day and decrease anxiety at night. Which of the following is a diagnostic criterion for a substance use disorder according to the DSM-5?
   A. Repeated drug use both alone and in interpersonal settings
   B. Experiencing cravings or urges to use the substance
   C. Having been legally prosecuted or arrested in possession of the substance
   D. Significant interpersonal problems (e.g., verbal or physical fights with friends or in intimate relationships)
   E. The substance has been taken at least once at the level of intoxication

   Correct Answer: B

   Continued use alone is not a criterion and does not necessarily indicate problem use unless the use results in interpersonal problems (A). Similarly having significant interpersonal problems, including fights, is not a criterion itself unless it is tied to substance use (i.e., the person was under the influence when fighting, the fight resulted from wanting to acquire substance, etc.) (D). Unless the legal problem or arrest is associated with documented intoxication, this would not constitute a diagnostic criterion based on DSM-5. The DSM-IV diagnosis of substance abuse included the language in answer choice C above. High level of use, including intoxication, does not constitute a criterion for SUD unless it persistent or there is evidence of tolerance (E).

4. Hannah is a 32-year-old lawyer, who has been enjoying a blossoming career for the past 3 years, since she finished law school. She has been enjoying going out for a drink or two after work with her colleagues. It helps her to wind down. Based on these descriptions, which cluster of symptoms that Hannah endorses would meet criteria for an SUD?

A. Patient endorses mild to moderate use of the substance. Her girlfriend has recently broken up with her because she would not stop drinking, which has been a recurrent problem in their relationship.
B. Patient has recently been seen in the ER with severe alcohol intoxication and withdrawal symptoms. She stated that she is going through a rough time at work having taken up a very stressful criminal case, which led her to want to "let loose" and binge drink with her friends during the weekend.
C. Patient is experiencing frequent cravings for the substance. She is anxious and depressed because she has alienated a lot of her friends and family members because of her alcohol use.
D. Patient has been taking substance in increasingly larger amounts. Despite having successfully stopped drinking during the month of January, she is worried she may have a problem with alcohol. She denies any psychological or physical effect of the substance he is consuming.
E. Patient had a recent documented DUI after she was driving while intoxicated. She has also a recent history of verbal altercations at work with some of her senior colleagues, whom have been commenting on her performance in her back.

Correct Answer: C

There is both evidence of persistent craving/urges and interpersonal problems resulting from the drug use (meets 2 criteria, which would qualify for mild SUD). Other options include one diagnostic criterion at the most, including potential relationship/interpersonal related to drug use (A), taking substance in increasing large amounts (D). Intoxication alone (B), DUI, or interpersonal conflicts which occur independently of using (E) are not criteria and may not necessarily point to an SUD diagnosis.

References

1. Sullivan E, Rosenbloom MJ, Pfefferbaum A. Pattern of motor and cognitive deficits in detoxified alcoholic men. Alcohol Clin Exp Res. 2000;24(5):611–21.
2. Samet S, Waxman R, Hatzenbuehler M, Hasin DS. Assessing addiction: concepts and instruments. Addict Sci Clin Pract. 2007;4(1):19.
3. Mitchell SG, Kelly SM, Gryczynski J, Myers CP, O'Grady KE, Kirk AS, et al. The CRAFFT cut-points and DSM-5 criteria for alcohol and other drugs: a reevaluation and reexamination. Subst Abus. 2014;35(4):376–80.
4. Ewing JA. Detecting alcoholism: the CAGE questionnaire. JAMA. 1984;252(14):1905–7.
5. Alcoholism NIoAAa. Recommended alcohol questions. 2003. Available from: http://www.niaaa.nih.gov/research/guidelines-and-resources/recommendedalcohol-questions.
6. Group WAW. The alcohol, smoking and substance involvement screening test (ASSIST): development, reliability and feasibility. Addiction. 2002;97(9):1183–94.
7. Saunders JB, Aasland OG, Babor TF, De la Fuente JR, Grant M. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. Addiction. 1993;88(6):791–804.
8. Selzer ML. The Michigan alcoholism screening test: the quest for a new diagnostic instrument. Am J Psychiatr. 1971;127(12):1653–8.

9. Skinner H. The drug abuse screening test (DAST): guidelines for administration and scoring. Toronto: Addiction Research Foundation; 1982.
10. Swartz MS, Perkins DO, Stroup TS, McEvoy JP, Nieri JM, Haak DC. Assessing clinical and functional outcomes in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial. Schizophr Bull. 2003;29(1):33–43.
11. Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. Ann Fam Med. 2009;7(4):357–63.
12. Butcher JN, Graham JR, Williams CL, Ben-Porath YS. Development and use of the MMPI-2 content scales. Minneapolis: University of Minnesota Press; 1990.
13. Millon T. Millon clinical multiaxial inventory-III. Manual 2nd ed. Bloomington: Pearson Assessments; 1997.
14. Morey LC. Essentials of PAI assessment. Hoboken: Wiley; 2003.
15. Hasin DS, O'Brien CP, Auriacombe M, Borges G, Bucholz K, Budney A, et al. DSM-5 criteria for substance use disorders: recommendations and rationale. Am J Psychiatr. 2013;170(8):834–51.
16. Staff CRE. Drinking patterns and their definitions. Alcohol Res. 2018;39(1):17.
17. Del Vecchio P. SAMHSA's working definition of recovery updated. 23–30 Mar 2012. Available from: http://blog.samhsa.gov/2012/03/23/samhsas-working-definition-of-recovery-updated.
18. Quello SB, Brady KT, Sonne SC. Mood disorders and substance use disorder: a complex comorbidity. Sci Pract Perspect. 2005;3(1):13.
19. Kendler KS, Davis CG, Kessler RC. The familial aggregation of common psychiatric and substance use disorders in the National Comorbidity Survey: a family history study. Br J Psychiatry. 1997;170(6):541–8.

Psychosocial Treatment of Substance Use Disorders

5

Natassia Gaznick and Patricia A. Judd

High-Yield Review Points

- Cognitive and behavioral therapies assume that thoughts, feelings, and behaviors are interdependent, and as such, altering one will influence the other.
- Mutual support therapies encourage reliance on fellow members and accepting responsibility for substance use and addictive behaviors through informational, emotional, and social support.
- Systems-based therapies encourage not only the evaluation of the transactions between the patient and his/her support system but also the involvement of that support system in the reinforcement of positive changes.
- Psychodynamic approaches can be integrated with cognitive, behavioral, mutual support, and pharmacological approaches to enhance treatment.

Introduction

Psychotherapeutic treatment for substance use disorders (SUDs) and behavioral addictions have been studied and applied in numerous treatment settings to a wide variety of patient populations. Each treatment described here has been shown to be efficacious in either reduction in or abstinence from the addictive behavior. Many interventions are aimed at accepting the addictive behavior and making steps toward reduction of response or exposure to triggers, whether internal or external. While each aims to have a unique element, these treatments can be roughly grouped based on their underlying psychological theories. These include cognitive, behavioral, mindfulness, motivation, mutual support, psychodynamic, and systems theory.

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Based on cognitive and/or behavioral theories, cognitive behavioral therapy (CBT), contingency management (CM), and mindfulness-based therapies are well studied in addiction literature. Originating in the behavioral theories of Pavlov, Watson, Skinner, and Bandura, behavioral approaches aim to uncouple the stimulus–response patterns evoked by substance use or other maladaptive behaviors. Cognitive approaches, based highly in Ellis and Beck, aim to maximize one's appreciation of how thoughts, feelings, and behaviors impact addictive behavior. Mindfulness aims to bring attention to the present moment without judgment. Placed on a spectrum, CM relies mostly on behavior, CBT on behavior and cognition, and mindfulness-based therapies on behavior, cognition, and mindfulness.

Psychodynamic, motivational, mutual help, and systems-based therapies aim to decrease addictive behaviors through understanding one's inner life and interpersonal relationships. The psychodynamic perspective involves the therapist developing an understanding of the patient and, in turn, helping the patient to understand the self in order to actualize change. Motivation has been shown to be a critical part of engagement and participation in treatment. Through examining biological, psychological, and social dimensions, in motivation-based interventions, the practitioner guides the patient to identify personal motivations for change. Miller and Rollnick developed the most well-known techniques and style aimed to help an individual move through the stages of change. Mutual help groups, led either by clinician or group member, are highly accessible and emphasize personal growth and fellowship as steps to develop self-efficacy and more effective coping behaviors. Systems-based therapies operate on the principle that change in one part of the system can produce change in another, whether these contribute to or help solve the problem. Systems-based therapies identify who is important to and involved in the patient's life and work in order to help change maladaptive patterns in the relationships that perpetuate addictive behavior.

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) is a structured and time-limited intervention that draws on both behavioral and cognitive theories with the aim of understanding and disrupting learned patterns associated with drug and alcohol craving and use. Known as "second wave" therapy (after the "first wave" of behavioral therapy), CBT assumes that psychological distress arises from maladaptive thought processes (cognitions) and behaviors. Thoughts, feelings, and behaviors are interdependent, and as such, altering thought patterns can influence feelings and behaviors. There are a number of common maladaptive thought processes and beliefs in people with SUDs, including all-or-nothing thinking, denial, and the belief that change is too difficult [1]. CBT for substance use disorders aims to reduce drug use by identifying and altering behaviors and thought processes leading to substance use and finding ways to manage unhelpful thoughts and feelings associated with high-risk behaviors. The therapist functions as an educator and guide who leads the patient in a functional analysis of substance use and individualized cognitive and behavioral skills training.

Empiric Evidence

Evidence supports the use of CBT for the treatment of multiple types of substance use disorders including alcohol, cannabis, cocaine, and nicotine [2, 3]. Commonly studied and implemented CBT includes 12–16 sessions conducted over about 12 weeks. It has been shown effective as a stand-alone treatment and in combination with medication and other therapeutic modalities. Studies have shown superiority of CBT in reduction of substance use at long-term follow-up, likely due to the durability of the skills learned, as those who complete homework during the course of CBT are more likely to stay in treatment longer, have more consecutive days of abstinence, and fewer positive drug screens [4].

For Whom

Adaptations of CBT are applicable for many types of persons and in a variety of treatment settings. While originally conceptualized as an outpatient treatment, this intervention may also be used in the inpatient setting or in group-based treatment. Despite the wide audience and settings, there are some clients who may be inappropriate for a standardized outpatient CBT, including those with cognitive deficits, medical or social stressors, and lack of social resources [5].

Motivation-Based Therapies

Motivation for change is a critical component for the successful treatment of addictive behaviors. The process of change involves addressing the biopsychosocial dimensions that maintain substance use and addictive behaviors, and as such, motivation-based treatments aim to facilitate change by identifying an individual's personal values and reasons for change. Motivation-based interventions were developed to foster provider-patient relationships that stimulate the individual's process of change.

Motivational interviewing (MI) is an interactive style of communication that encourages patients to talk themselves into change based on their own values. The spirit of MI includes partnership, acceptance, compassion, and evocation between the provider and patient in a guiding rather than directing style [6]. The core microskills for the practitioner include open-ended questions, affirmations, reflections, summaries, and informing/advising. MI has been adapted to brief interventions, use in primary care, and structured motivational enhancement therapy (MET).

MET is a structured therapy, initially developed for research studies, that combines MI and normative feedback, which compares the patient's behaviors with population norms. MET is a manualized version of MI that consists of an assessment battery and additional sessions designed to elicit change in a short timeframe. As described for Project MATCH, a 5-year NIAAA study for the treatment of alcohol use disorder, MET was initially developed as four focused sessions; the first two

focused on structured feedback from the assessment, future plans, and motivation for change, and the second two focused on reinforcing progress, encouraging reassessment, and providing an objective perspective on change [7].

Empiric Evidence

Studies evaluating MET in alcohol use have demonstrated that despite its less intensive nature, MET has equivalent effects on frequency and intensity of alcohol consumption compared to more intensive treatments at 1- and 3-year follow-up [8]. MET in combination with CBT has been successful in treating cannabis-dependent adults, and results are mixed for the use of MET with other drugs of abuse. Other studies, however, suggest MI/MET may be more effective at short-term follow-up with diminishing strength over time in the absence of other modalities [9].

For Whom

Patients who may benefit from MI include those without explicit reasons for change and those with difficulty resolving their ambivalence about the addictive behavior. While studies have demonstrated efficacy in pregnant women, adolescents, and those with co-occurring disorders, MI/MET appears most effective in engaging patients in treatment rather than in providing skills to elicit large-scale behavioral changes. Additionally, MET may be more effective than CBT or 12-step facilitation in patients with a high degree of anger who are undergoing treatment for alcohol use disorder [10].

Contingency Management

Contingency management (CM) is based on operant learning and aims to increase the positive consequences of abstinence through timely extrinsic motivators for behavior change. CM uses monetary-based and other reinforcements as reward behaviors including demonstration of abstinence, treatment attendance, and medication adherence. Three key principles in the implementation of CM strategies include (1) frequent behavior monitoring, (2) immediate disbursement of tangible positive reinforcements, and (3) denial of positive reinforcements without the target behavior [11]. Monitoring involves objective assessments, and when reward is based on drug use, it should be tailored to the frequency of drug use and the ability of the test to detect the target drug. Positive reinforcements are commonly prizes or vouchers for goods/services rather than actual monetary rewards due to treatment programs' financial limitations. Rewards can use escalating reinforcement, which involve increasing prize/voucher amount with increasing number of desired behaviors, as this promotes longer durations of abstinence and long-term success. Importantly, the positive reinforcements are withheld and reset back to starting value when the target behavior is not met.

Empiric Evidence

CM is well studied for multiple substances and treatment outcomes. Clinical trials and meta-analyses have demonstrated effectiveness in treating individuals with stimulant (cocaine and methamphetamine), nicotine, alcohol, opioid, cannabis, and sedative (benzodiazepine) use disorders [12]. Evidence has shown superiority of CM to standard treatment conditions for short-term abstinence, treatment retention, and attendance in therapy [13]. However, data are mixed on the utility of CM in long-term abstinence, as there is contention regarding the ability of extrinsic motivators to improve intrinsic motivation for long-term change [11].

For Whom

The patients and treatment settings that may benefit from CM are quite broad. Studies support use in broad socioeconomic, demographic, and mental health populations. There are, however, some instances in which CM may not be optimal. Those that may benefit less from CM include patients with extrinsic motivators elsewhere (e.g., those in the criminal justice system). Clinics or payers with limited funding or no mechanism to provide reinforcements may have limited systems-level support to provide rewards. Additionally, reliance on qualitative drug screens would make the use of CM problematic in harm reduction models, as it would require a quantitative test to measure a decrease in use rather than complete abstinence.

Mindfulness-Based Therapies

Mindfulness-based therapies (MBT) integrate traditional Buddhist practices with current psychological practice as part of the "third wave" of cognitive and behavioral therapies. The cognitive aspect of mindfulness aims to enhance one's attention to self and environment in a nonjudgmental manner and includes noticing thoughts and feelings without challenging the content. The behavior aspect aims to strengthen one's ability to experience triggers without defaulting to unhelpful habits. Although initially utilized in treating depression, mindfulness-based treatments have grown in popularity and are accepted as treatment for substance use disorders and behavioral addictions.

Mindfulness-based relapse prevention (MBRP) is an 8-week manualized outpatient program designed to decrease relapse through increasing awareness of and flexibility to triggers for substance use. The therapy begins with two sessions to introduce the rationale of the therapy and the goal of increasing awareness of external triggers and individual thoughts, feelings, and behaviors that may contribute to relapse. Clients then engage in exercises to strengthen mindfulness in daily life and in high-risk situations, to accept current situations, to see thoughts apart from actions, to improve self-care, and to improve social support [14].

Mindfulness-oriented recovery enhancement (MORE), which is similar to MBRP, has its roots in mindfulness and CBT; however, it also draws from positive psychology. It is a strength-based intervention with foundations in cognitive control of (1) attention through mindfulness (as described above), (2) negative emotion through reappraisal (reinterpreting stress), and (3) reward processing through savoring (focusing on positive present events). MORE was originally designed as a 10-session protocol that address mindfulness, automatic habits, reappraisal, savoring, craving, coping with stress, attachment versus aversion, body impermanence, relationships, meaning, and future orientation.

Empiric Evidence

Mindfulness-based treatment has been shown to be effective in the treatment of alcohol, tobacco, cocaine, amphetamines, cannabis, opiates, and behavioral addictions [15]. MBTs show small to large effect sizes in reducing the frequency and severity of substance use, craving, and stress in those with substance use disorders [16]. A main hypothesis for the effectiveness of MBT is that these therapies improve reactivity to craving cues, possibly through improvement in emotion regulation, decrease in perceived stress, and decrease in stress reactivity [15]. Studies have shown that individuals most frequently rated the "stop observe breathe expand respond (SOBER) breathing space" exercise, which improves proactive rather than reactive behaviors in MBRP, as one of the key elements in helping to maintain sobriety [14].

For Whom

MBTs have been shown to be beneficial in diverse treatment settings and to a diverse population of adults. MBTs may be carried out in either the inpatient or outpatient setting. While many manualized MBTs are closed-group, MBTs may be carried out in individual therapy. Of note, MBT for substances has been beneficial in incarcerated populations and adolescents, but more research is needed [16]. It may be especially helpful in female populations, as women are more likely to relapse due to negative emotions, and those with comorbid depression, as MBTs can improve self-esteem and mood in the setting of difficult experiences [14].

Psychodynamic Psychotherapy

Individual psychodynamic therapy can be useful in the treatment of substance use disorders in combination with medication-assisted treatment, group and family therapy and mutual support groups. Its goal is enhanced self-understanding and improved self-reflective capacity. It can also assist patients in accepting that they suffer from addiction and can be used to maintain progress. However,

understanding alone does not result in sobriety. Psychodynamic perspectives view addiction as (1) a special adaptation to developmental challenges, (2) an attempt to self-medicate painful emotions, (3) a primary problem in self-regulation, and (4) a reflection of disorder in personality organization [17]. Modern psychodynamic approaches help patients to identify how their past relationships influence current behaviors and may drive substance use as a coping strategy. It helps to build a stronger sense of self, improve affect regulation, and promote personality integration.

Sessions are generally held one to three times per week for 45 minutes, and the treatment usually spans several years. Therapists monitor the patient-therapist relationship and use it as a means for understanding the self, and as a vehicle through which to discuss and understand disjunctions and misalliances.

Empiric Evidence

To date there are no controlled studies of traditional long-term psychodynamic treatment of substance use disorders. There are a number of brief psychodynamic therapies, and of these, supportive-expressive (SE) and interpersonal (IPT) have been studied with success for use with substance use disorders [18].

For Whom

This approach is indicated for treatment-resistant patients, individuals with comorbid personality disorders, and those who wish for privacy and/or have difficulty with mutual support groups. Patients with high intelligence, a capacity for intimacy, motivation to find meaning in their behavior, and/or a beginning capacity for self-reflection may do well with psychodynamic approaches [19].

Mutual Aid Groups

Mutual aid (also called mutual support, mutual help) approaches are based on individuals changing addictive behavior without the use of health professionals. Mutual support groups are recovery-oriented, nonprofessional groups that rely on their members to support one another by encouraging responsibility for substance use through informational, emotional, and social support for persons with a substance use disorder and their families. There are a number of mutual aid approaches, including 12-step Groups, Women for Sobriety (WFS), and SMART Recovery® (Self-Management and Recovery Training).

Twelve-step groups, as initially outlined by Alcoholics Anonymous (AA), have been developed for a number of substance and behavioral addictions with the goal of abstinence through a series of 12 “steps.” These focus on admitting powerlessness of the user over drugs and alcohol (not over everything in their

life, that is, saying that even a small amount of use becomes out of control), exploring past wrongs and the causal character traits, seeking forgiveness for past wrongs, seeking connection to a higher power, and carrying forward these strategies to others who suffer. Twelve-step groups nurture self-worth through prosocial behavior norms (helping others, engaging in service work), connecting with spirituality, and celebrating sobriety milestones. The participants are encouraged to develop a relationship with a sponsor, who is generally a senior member with long-term abstinence who is willing to lead the participant through ("work") the steps. Groups exist for individuals with alcohol, nicotine, narcotics, cocaine, methamphetamine, and dual diagnosis disorders, as well as for family members (e.g., Families Anonymous, Al-Anon/Alateen, Nar-Anon, and Co-Anon).

While not a mutual aid group itself, 12-step facilitation (TSF) is a manualized therapy led by a clinician to help a patient begin and/or attend 12-step meetings through integration of principles offered in 12-step meetings with medication and psychotherapy for substance use disorders. The three main ideas in TSF include acceptance of addiction as chronic and progressive, surrender to a higher power, and involvement in 12-step meetings.

Women for Sobriety (WFS) is one of the oldest mutual aid programs and was founded as an alternative to traditional 12-step therapy based on the idea that women require a different approach to achieve and maintain sobriety. It focuses on nurturing self-worth through its "New Life" Program. WFS utilizes 13 acceptance statements and six levels of recovery to promote behavioral change through a cognitive, behavioral, mindful, and group approach to addictive behaviors.

SMART Recovery® (Self-Management and Recovery Training) utilizes CBT-based rational emotive behavior therapy (REBT) to reverse self-destructive behavior through managing thoughts and feelings that are associated with substance use or behavioral addictions. Through their "4-point Program," SMART aims to enhance motivation and assist the participant in refusing to act on urges, using coping skills, and developing a balanced lifestyle. Similar to CBT, SMART emphasizes skills training and discussion in the group. Unlike 12-step, SMART does not encourage reliance on a higher power or the notion of "powerlessness," supports graduation from the program, accepts harmful behavior reduction as a goal, and can be led by a facilitator not in recovery.

Empirical Support

Numerous studies have shown that involvement in 12-step groups is associated with greater rates of abstinence and other recovery outcomes in the treatment of alcohol use disorder and other substances. Studies involving TSF support its utility in increasing membership in 12-step groups and odds of abstinence [20]. WFS and SMART have shown to be as effective as 12-step groups for those with AUD as the traditional 12-step approach when taking into account abstinence goals [21].

For Whom

Mutual aid is a group-based treatment utilized in both inpatient and outpatient recovery. Due to the element of the "higher power," traditional 12-step groups may not be ideal for those with an opposition to its focus on spirituality. TSF has been shown to be helpful in the treatment of alcohol use disorder and may be especially helpful for those with dual diagnoses, as TSF encourages the practitioner to incorporate integrative care that is low cost and high frequency. This may facilitate treating underlying psychiatric illness contributing to substance use. Importantly, those with comorbid psychiatric disorders may have a more difficult time in traditional 12-step groups without formal support due to challenges associated with their psychiatric diagnosis or resistance from some groups at supporting use of psychotropic medications. Demographically, mutual support functions for adults of both sexes, but youth have a high dropout rate (this is true in youth across modalities).

Systems-Based Therapy

Systems-based therapies aim to influence substance use through acknowledging, examining, and utilizing the relationships between an individual and their membership in various groups (systems).

Family-Based Treatments

Substance use disorders result from a transaction among multiple individual, genetic, family, and community factors. Factors such as parent psychopathology, relational distance, family conflict, and inadequate parenting are predictors of substance use initiation and maintenance [22]. In turn, substance use seriously impacts family functioning and relationships. Because of these transactions, family therapy has been found to be an important intervention that can facilitate engagement and maintenance in treatment and prevent or minimize relapse.

The focus of family therapy is to intervene in complex relational patterns and to alter them in ways that bring about productive change for the entire family. Family therapy rests on systems theory, which proposes that changes in one part of the system can and do produce changes in other parts of the system, and these changes can improve functioning.

Family-based approaches include separate treatments, each with its own conceptual framework and evidence base. The approaches with the strongest empirical support include (1) brief strategic family therapy (BSFT) [23], based in family systems theory that targets adolescents' substance use and other challenging behaviors by facilitating changes in the family's patterns of interaction; (2) multisystemic therapy (MST) [24], rooted in a social ecology perspective that addresses the risk/protective factors (e.g., family, peer group, school, and neighborhood) that influence substance use behavior among adolescents; (3) multidimensional family therapy

(MDFT) [25] that addresses substance use and problematic behaviors in adolescents by intervening on a number of levels similar to MST and integrates family therapy, the social ecology perspective, and developmental psychology; and (4) functional family therapy (FFT) [26] that evolved from both behavioral and systems-oriented theoretical approaches and whose goal is to enhance communication and support within the family while altering maladaptive familial patterns.

Behavioral Couples Therapy

The most well-developed and studied couples approach is behavioral couples therapy [27]. It involves an initial agreement for the person misusing substances to commit to sobriety and the partner to reinforce this commitment daily. It also teaches strategies to cope with cravings, manage relapse, communicate, and engage in pleasurable activities together.

Empiric Evidence

Family approaches appear to be the most effective for adolescents compared to treatment as usual [28]. Evidence also supports the use of BSFT, MDFT, and MST family approaches with ethnic minority youth and their families [29]. A meta-analysis of 12 behavioral couples therapy trials found that the model achieved an average medium effect size over individual comparison treatments with strong effects at follow-up points [30].

For Whom

Family involvement in treatment is optimal when working with adolescents. It is also strongly recommended when the client is living within a family system, for example, as a couple or single parent or both parents and children. Modifying harmful family patterns can facilitate change behavior and prevent relapse. Family members need support and education as to how to cope with the behaviors of their loved one and how to communicate effectively so that even if therapy is not available, the family can be brought in for education and support sessions. The challenge lies in finding staff who are trained in general family and/or couples therapy since many of the approaches have been manualized and require specific training.

Matrix Model

The Matrix model combines elements of family approaches, 12-step facilitation, and relapse prevention and was originally designed to treat methamphetamine addiction within an intensive outpatient program. The current model includes three individual or conjoint family sessions and 52 group sessions over 16 weeks.

Clients are asked to participate in social support groups weekly during the aftercare phase [31].

For Whom

This treatment was designed for those suffering from methamphetamine misuse but has been expanded to those with substance use disorders who can benefit from an intensive outpatient program (IOP). Staff must be fully trained in the methodology, and clients must be able to access IOP level treatment.

Empiric Evidence

A multisite study comparing the Matrix model to treatment as usual was conducted in eight community treatment programs for those struggling with methamphetamine misuse [32]. There were no differences at follow up in substance use or psychosocial functioning at discharge or 6 months. However, Matrix model participants had better retention and completion rates.

Community Reinforcement and Family Training (CRAFT)

CRAFT is an outgrowth of the "community reinforcement training" or CRT. It is a skills-based program that impacts families in multiple areas of their lives, including self-care, pleasurable activities, domestic violence precautions, problem-solving, and goal setting. CRAFT addresses the loved one's resistance to change. It teaches families behavioral and motivational strategies for interacting with their loved one. Participants learn the power of positive reinforcement for positive behavior and of withdrawing it for unwanted behavior, as well as how to use positive communication skills to improve interactions and maximize their influence [33].

Empiric Evidence

CRAFT was found to be superior in engaging treatment-resistant individuals compared to traditional programs, demonstrating three times more patient engagement than Al-Anon. CRAFT encouraged two-thirds of treatment-resistant individuals to attend four to six CRAFT sessions [34].

Review Questions

1. A new patient is seeking a therapy that will help her to decrease cue-induced cravings and help her be more proactive rather than reactive. Which of the following therapies focuses on combining traditional Buddhist ideology with

modern psychological theory to focus on strength-based cognitive control through mindfulness for the treatment of addictive behaviors?

A. Motivational enhancement therapy
B. Mindfulness-oriented recovery enhancement
C. Cognitive behavioral therapy
D. 12-step facilitation
E. SMART recovery

Correct Answer: B

Explanation: Similar to traditional behavioral approaches, mindfulness-oriented recovery enhancement examines thoughts, feelings, and behaviors, but it also uses the Buddhist approach of acceptance rather than challenging what arises in the mind and body.

Reference: Witkiewitz K, Bowen S, Harrop EN, Douglas H, Enkema M, Sedgwick C. Mindfulness-based treatment to prevent addictive behavior relapse: theoretical models and hypothesized mechanisms of change. Subst Use Misuse. 2014;49(5):513–24.

2. A 27-year-old male with a stimulant use disorder tells you that he learns best through positive rewards rather than thinking through problems. You consider contingency management, which uses external motivation for abstinence through translating long-term positive consequences for clinically relevant positive behaviors into immediate ones. This is an application of which of the following psychological theories?

A. Behavioral
B. Cognitive
C. Mindfulness
D. Systems
E. Psychoanalytic

Correct Answer: A

Explanation: Behavioral theory posits that the stimulus–response patterns elicited by substance use can be replaced by positive consequences of abstinence. Cognitive and systems theory rely on functional analysis of substance use for the individual (cognitive) or group (systems). Mindfulness focuses on uncoupling triggers with unhelpful habits. Psychoanalytic theory involves self-understanding and reflection.

Reference: Walter KN, Petry NM. Motivation and contingency management treatments for substance use disorders. In: Simpson E, Balsam P, editors. Current topics in behavioral neurosciences, vol 27. Cham: Springer; 2015. p. 569–81.

3. Despite meeting criteria for alcohol use disorder, a new intake is struggling to see how his substance use is a problem while he drinks the same amount as his friends. Which structured therapy might help the patient find reasons for change not only based on his life circumstances but also normative feedback?

A. Twelve-step facilitation
B. Mindfulness-based relapse prevention

C. Cognitive behavioral therapy
D. Community reinforcement and family training
E. Motivational enhancement therapy

Correct Answer: E

Explanation: Motivational enhancement therapy utilizes the spirit and skills of MI to help patients talk themselves into change, while providing real-world data on their drug use patterns, negative life consequences, level of functioning and depression, and where the patient is in terms of motivation for change. Twelve-step facilitation promotes acceptance of addiction through integrating ideas of 12-step groups such as powerlessness, a higher power, and sponsorship. The other choices are skills based and do not explicitly focus on either motivations for change or assessments of use and functioning.

4. A 55-year-old male is being treated on a 30-day inpatient rehabilitation unit using contingency management for his methamphetamine use. He receives vouchers for abstinence, medication adherence, and attending individual and group sessions. Which of the following is in line with the key principles of contingency Management?
   A. Urine drug screen only on admission and discharge
   B. Immediate disbursement of reward voucher for medication adherence
   C. Subjective assessment of drug use
   D. Added clean-up duties for missing group sessions
   E. De-escalating rewards with increased number of days abstinent

   Correct Answer: B

   Explanation: Contingency management aims to increase the positive consequences of abstinence. When monitoring drug use, it is important to tailor monitoring to the ability of the test to detect the target drug, so any use within the 30 days may not be detected on discharge. Monitoring should involve objective assessments, such as urine drug screen. Rather than present new punishments for missing target behavior, positive reinforcers are withheld and reset. When target behaviors are met continuously, rewards can be increased to promote longer duration of behavior.

   Reference: Walter KN, Petry NM. Motivation and contingency management treatments for substance use disorders. In: Simpson E, Balsam P, editors. Current topics in behavioral neurosciences, vol 27. Cham: Springer; 2015. p. 569–81.

5. A 65-year-old English Professor comes to your clinic asking for advice on which type of psychotherapy might be most helpful for treating his alcohol use disorder in combination with beginning his medication assisted treatment. You find he has been drinking to cope with his daughter's death and is struggling to find meaning in his life, but has a great ability to self-reflect and a supportive spouse. He does not want to go to a group because he feels he will not fit in and is worried about colleagues finding out. Which type of psychotherapy would you recommend?
   A. Matrix model
   B. SMART recovery

C. Mindfulness-based relapse prevention
D. Psychodynamic psychotherapy
E. Motivational interviewing

Correct Answer: D

Explanation: Psychodynamics may be best suited for those, like this patient, who seek confidentiality, have high intelligence, and have capacity for self-reflection. He would likely not wish to participate in the Matrix model or SMART, as those are group-based. Mindfulness-based relapse prevention is best for individuals who have undergone initial treatment. The patient is already motivated for change and ready to take action, so MI may not be useful in this situation.

Reference: Lightdale HA, Mack AH, Frances RJ. Psychodynamic psychotherapy. In: Galanter M, Kleber HD, Brady K, editors. Textbook of substance abuse treatment. 5th ed. Washington, DC: American Psychiatric Publishing Co; 2015. p. 365–84.

References

1. Ellis A, McInerney JF, DiGiuseppe R, Yeager RJ. Rational-emotive therapy with alcoholics and substance abusers. Elmsford: Pergamon Press; 1988.
2. Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW. A meta-analytic review of psychosocial interventions for substance use disorders. Am J Psychiatry. 2008;165(2):179–87.
3. Magill M, Ray LA. Cognitive-behavioral treatment with adult alcohol and illicit drug users: a meta-analysis of randomized controlled trials. J Stud Alcohol Drugs. 2015;70(4):516–27.
4. Carroll KM, Nich C, Ball SA. Practice makes progress? Homework assignments and outcome in treatment of cocaine dependence. J Consult Clin Psychol. 2005;73(4):749–55.
5. McHugh RK, Hearon BA, Otto MW. Cognitive behavioral therapy for substance use disorders. Psychiatr Clin North Am. 2010;33(3):511–25.
6. Miller WR, Rollnick S. Motivational interviewing: helping people change. 3rd ed. New York: Guilford Press; 2013. 482 p.
7. Miller WR. Motivational enhancement therapy manual: a clinical research guide for therapists treating individuals with alcohol abuse and dependence. Rockville: Diane Publishing Company; 1995.
8. Miller WR, Zweben A, DiClemente CC, Rychtarik R. Motivational enhancement therapy manual: a clinical research guide for therapists treating individuals with alcohol abuse and dependence. Project MATCH monograph series 2 (SHHA Publ No ADM-92-1884). National Institute on Alcohol Abuse and Alcoholism: Rockville; 1992.
9. DiClemente C, Greene P, Petersen A, Thrash S, Crouch T. Motivational enhancement. In: Galanter M, Kleber HD, Brady KT, editors. The American Psychiatric Publishing textbook of substance abuse treatment. 5th ed. Arlington: American Psychiatric Publishing; 2015. p. 397–409.
10. Project MATCH Research Group. Matching alcoholism treatments to client heterogeneity: project MATCH three-year drinking outcomes. Alcohol Clin Exp Res. 1998;22(6):1300–11.
11. Walter KN, Petry NM. Motivation and contingency management treatments for substance use disorders. In: Simpson E, Balsam P, editors. Current topics in behavioral neurosciences, vol. 27. Cham: Springer; 2015. p. 569–81.

12. Prendergast M, Podus D, Finney J, Greenwell L, Roll J. Contingency management for treatment of substance use disorders: a meta-analysis. Addiction. 2006;101(11):1546–60.
13. Petry NM. Contingency management treatments: controversies and challenges. Addiction. 2010;105(9):1507–9.
14. Witkiewitz K, Bowen S, Harrop EN, Douglas H, Enkema M, Sedgwick C. Mindfulness-based treatment to prevent addictive behavior relapse: theoretical models and hypothesized mechanisms of change. Subst Use Misuse. 2014;49(5):513–24.
15. Garland EL, Howard MO. Mindfulness-based treatment of addiction: current state of the field and envisioning the next wave of research. Addict Sci Clin Pract. 2018;13(1):14.
16. Li W, Howard MO, Garland EL, McGovern P, Lazar M. Mindfulness treatment for substance misuse: a systematic review and meta-analysis. J Subst Abus Treat. 2017;1(75):62–96.
17. Khantzian EJ. Understanding addictive vulnerability: an evolving psychodynamic perspective. Neuropsychoanalysis. 2003;5(1):5–21.
18. Center for Substance Abuse Treatment. Brief interventions and brief therapies for substance abuse. Treatment improvement protocol (TIP) series, No. 34. HHS publication No. (SMA) 12-3952. Rockville: Substance Abuse and Mental Health Services Administration; 1999.
19. Lightdale HA, Mack AH, Frances RJ. Psychodynamic psychotherapy. In: Galanter M, Kleber HD, Brady K, editors. Textbook of substance abuse treatment. 5th ed. Washington, DC: American Psychiatric Publishing Co; 2015. p. 365–84.
20. Zemore SE, Kaskutas LA, Mericle A, Hemberg J. Comparison of 12-step groups to mutual help alternatives for AUD in a large, national study: differences in membership characteristics and group participation, cohesion, and satisfaction. J Subst Abus Treat. 2017;73:16–26.
21. Zemore SE, Lui C, Mericle A, Hemberg J, Kaskutas LA. A longitudinal study of the comparative efficacy of Women for Sobriety, LifeRing, SMART recovery, and 12-step groups for those with AUD. J Subst Abus Treat. 2018;88:18–26.
22. Tobler AL, Komro KA. Trajectories or parental monitoring and communication and effects on drug use among urban young adolescents. J Adolesc Health. 2010;46(6):560–8.
23. Szapoczink J, Hervies O, Schwartz S. Therapy manuals for drug addiction. Manual 5. Brief strategic family therapy for adolescent drug abuse. Bethesda: NIDA; 2003.
24. Henggeler SW, Borduin CM. Family therapy and beyond: a multisystemic approach to treating the behavior problems of children and adolescents. Pacific Grove: Brooks/Cole; 1990.
25. Liddle HA. Multidimensional family therapy for adolescent cannabis users. Cannabis youth treatment (CYT) series, vol. 5. Rockville: Center for Substance Abuse Treatment (CSAT); 2002.
26. Alexander J, Parsons BV. Functional family therapy. Monterey: Brooks/Cole Publishing Company; 1982. 188 p.
27. O'Farrell TJ, Fals-Stewart W. Behavioral couples therapy for alcoholism and drug abuse. New York: Guildford Press; 2006. 436 p.
28. Rowe CL. Family therapy for drug abuse: review and updates 2003–2010. J Marital Fam Ther. 2012;38(1):59–81.
29. Szapocznik J, Williams RA. Brief strategic family therapy: twenty-five years of interplay among theory, research and practice in adolescent behavior problems and drug abuse. Clin Child Fam Psychol Rev. 2000;3(2):117–34.
30. Powers MB, Vedel E, Emmelkamp PMG. Behavioral couples therapy (BCT) for alcohol and drug use disorders: a meta-analysis. Clin Psychol Rev. 2008;28(6):952–62.
31. Rawson R, McCann M. Counselor's treatment manual: matrix intensive outpatient treatment for people with stimulant use disorders. DHHS publication No. (SMA). Rockville: Substance Abuse and Mental Health Services Administration; 2006.
32. Rawson RA, Marinelli-Casey P, Anglin MD, Dickow A, Frazier Y, Gallagher C, et al. A multisite comparison of psychosocial approaches for the treatment of methamphetamine dependence. Addiction. 2004;99(6):708–17.
33. Meyers RJ, Miller WR, Hill DE, Tonigan JSS. Community reinforcement and family training (CRAFT): engaging unmotivated drug users in treatment. J Subst Abus. 1998;10(3):291–308.
34. Meyers RJ, Miller WR, Smith JE, Tonigan JS. A randomized trial of two methods for engaging treatment-refusing drug users through concerned significant others. J Consult Clin Psychol. 2002;70(5):1182–5.

Recovery from Addiction: Maintenance and Preventing Relapse

6

Ricardo Restrepo-Guzman, Danielle Li, and Grace Lynn

High-Yield Review Points

- Recovery is a process of change, not a static event, characterized by voluntarily maintained control over substance use, leading toward health and well-being.
- Abstinence is often a main goal of treatment, but it does not mean that it is the only measure of progress.
- Psychosocial interventions for SUDs target physical, behavioral, cognitive, emotional, interpersonal, and environmental factors to improve the overall functioning of the individual.
- The therapeutic intervention can facilitate the identification of triggers and cravings and how to address them.
- Understanding the process of relapse is vital to developing an effective relapse prevention plan.
- Relapse prevention is a treatment approach with the goal of preventing lapses or relapses by providing coping skills and alternatives to repeating previous unwanted behaviors.

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Definition of Recovery

Though various definitions exist for recovery from SUD, one of the most comprehensive comes from the Betty Ford Institute Consensus Panel, which characterizes *recovery* as "a voluntarily maintained lifestyle composed by sobriety, personal health, and citizenship." This definition encompasses abstinence from substance use, improvement in quality of health, and development of personal relationships. Other definitions focus more on the progression to sobriety, such as "remission, resolution, abstinence, and recovery," but all of these conceptualizations agree upon recovery as a state of living without impairments or negative consequences from substance use. Rather than a singular end point, recovery is a long-term, ongoing process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential [1].

Although there are various more detailed definitions of recovery from SUDs, all of these iterations agree that recovery goes beyond the remission of SUD symptoms to include a positive change in the whole person. In this regard, abstinence from substances, though often a necessary component, is not in itself sufficient to equate to recovery. Major points associated with the recovery-oriented approach include viewing SUDs as chronic rather than acute problems, emphasizing the long-term support that is required, and focusing on recovery management rather than disease management.

The four major dimensions that support a life in recovery are health, home, purpose of life, and community-oriented participation. Sustained recovery is self-directed and involves personal choices, the support of peers and allies, and community reinforcement as well as a strength-based approach and the use of research-based interventions [2].

Stages of Recovery

There are several ways of thinking about the recovery process. A common one, which is divided into five stages of change in recovery, is sometimes referred to as the transtheoretical model of change (TTM) [3] (Fig. 6.1).

Pre-contemplation Stage

This stage is typically characterized by denial of alcohol or drug addiction, with limited or no recognition of the negative consequences of their substance use. Perceived cons of quitting far outweigh pros of quitting. There is no intention to take action in the foreseeable future (i.e., in the next 6 months).

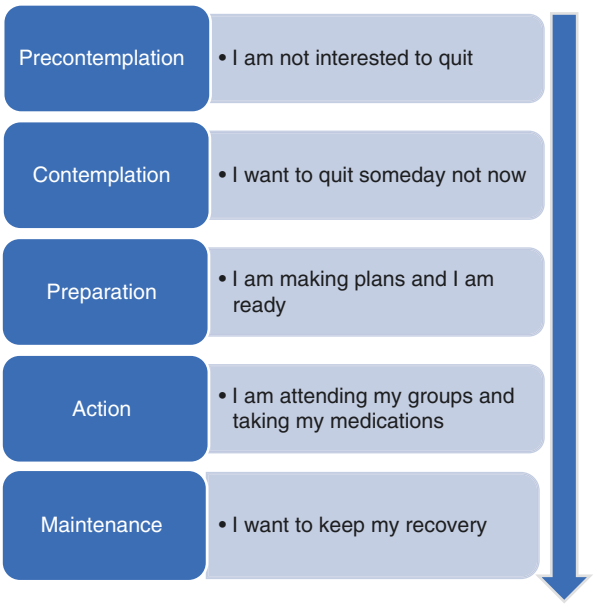

Fig. 6.1 Transtheoretical model of change (TTM)

Contemplation Stage

There is intent to make a healthy behavioral change in the foreseeable future. The patient recognizes negative consequences of the substance use and adopts a more balanced view of pros vs. cons of pursuing sobriety. However, some ambivalence may remain.

Preparation Stage

Readiness to take action within the next 30 days. The patient is already beginning to make small steps toward sobriety and has fully embraced the belief that sobriety can lead to a healthier and happier life.

Action Stage

The behavior change has been implemented within the last 6 months, and the patient intends to continue in this trajectory.

Maintenance and Relapse Prevention

The patient has sustained the behavioral change for more than 6 months, intends to maintain this, and is actively practicing RP techniques to avoid falling back to an earlier stage.

Pathways to Recovery

There are different pathways to recovery to choose from based on cultural values, socioeconomic status, psychological and behavioral needs, and the nature of the individual's SUD. Recovery can be achieved by combining various frameworks including secular, spiritual/religious, natural recovery, peer-assisted, treatment-assisted, abstinence-based, moderation-based, and medication-assisted treatment, among others. The experience and reconstruction are a constant process which needs to be individualized and not generalized. The combination of physical, cognitive, emotional, relational, and spiritual health across the stage of life is fundamental when measuring recovery.

Early Recovery: Monitoring for Treatment Adherence and Relapse

Prescription Drug Monitoring Programs

Prescription drug monitoring programs (PDMPs) in the United States are state-level databases that track prescriptions of controlled substances, and their role in the management of SUDs has become increasingly prominent with the rise of opioid use disorders. While the programs themselves may differ from state to state, in general they can serve a key role in clinical decision-making and prescribing. In the context of substance use treatment, PDMPs provide information about a patient's past and current prescribed controlled substances, allow for collaboration with the patient's other identified prescribers, and may identify concerning activity – for example, undisclosed benzodiazepine use while concurrently receiving buprenorphine treatment – that may not be detected in the snapshot of recent use that a urine drug test provides. Whether PDMP data is accessed as part of an initial intake assessment or a periodic check, a concerning finding is important to discuss with the patient for clarification and to arrive at a mutually agreed treatment plan that takes this information into account.

Toxicology

Notwithstanding the abovementioned caveat that urine drug tests are only a detector of recent use, both baseline and unscheduled drug testing are a key component of monitoring treatment adherence in relapse prevention, alongside risk stratification, behavioral assessment, and the PDMPs described in the previous section [4]. Periodic random urine drug tests can test for opioids, though a provider interpreting the results should have an understanding of the test's cut-off thresholds (consider false negatives), each drug of interest and its possible metabolites. Urine testing is also useful for benzodiazepines, particularly for patients on chronic opioid therapy given their high risk of adverse effects in combination. For alcohol use, a breathalyzer

test is a common affordable option, and urinary testing is also frequently used. Assaying for alcohol metabolites EtG and EtS allows for an extended window of detection for recent alcohol use, up to about 4 days after complete elimination of alcohol from the body, depending on the patient's use.

With all of the above tests, it is important for the provider to keep in mind that drug tests provide information about recent use of drugs, but do not, in themselves, identify SUDs or physical dependence. An unexpected positive drug test result or, in some cases, an unexpected negative drug test result, necessitates a careful evaluation and frank, nonjudgmental discussion with the individual. This can rule out false positives from a cross-reacting substance and foster open communication with the individual regarding adjustments to the treatment plan if needed. Similarly, important are communication and collaboration with the individual's other providers, particularly other prescribing providers. Talking with a person who has tested positive, rather than reflexively taking action, can prevent inappropriate reactions to a positive test result and begin a collaborative effort to solve a problem.

Measurement of Recovery: Measuring Success in Treatment

Recovery is multifaceted and involves various factors beyond cessation of substance use. It includes overcoming physical and psychological dependence on substances, as well as integration into society. The process of recovery is highly individualized, and this is likely the reason why there is no standardized measurement to determine successful treatment [5, 6]. Abstinence can be an end goal, but need not be the sole measure of progress. The individual may first be encouraged to identify small changes and how these can start to impact his or her well-being. Progress in recovery should be realistic and measured according to the individual's goals, as there can be a mismatch in clinician expectations for progress and the patient's own goals for his or her substance use recovery. Any positive change can be valued and reinforced by the clinician, such as through motivational interviewing skills. In the same vein, setbacks can be normalized without being minimized while continuing to work toward recovery and identifying positive changes. Reviewing progress in recovery goals at regular intervals is an integral part of a treatment plan. Treatment is dynamic, and changes can lead the team – comprised of the individual with SUD, clinicians and family members – to identify new goals and recovery strategies. As part of an effective approach, progress is not assessed in absolutes, but rather is discussed in an atmosphere where values, trust, and a humanitarian approach are practiced instead of authoritarianism, judgment, fear, and criticism.

Biopsychosocial Vulnerabilities Leading to SUD

Many factors contribute to vulnerability to the development of an SUD. Effective clinical care utilizes treatment that targets multiple considerations that contribute to the clinical presentation, including biological, genetic, psychological, social, and

cognitive components. A comprehensive treatment model can ultimately lower rates of relapse and enhance recovery. A few studies have stratified the risk of developing substance use disorder into the following: fixed risk factors (gender, ethnicity, family history, socioeconomic status), contextual risk factors (social norm, price controls/taxation, access laws), and individual/interpersonal risks (comorbid psychiatric disorders, history of trauma, family/peer relations, housing situation, employment, education, religion, marriage/parental roles) [7].

Family and twin studies demonstrate that approximately 50% of contribution to development of an SUD is genetic. Across cultures, males tend to have more substance use and disorders than females. Some ethnic minority groups (e.g., American Indians, African Americans, Hispanics) have disproportionately higher rates of substance use in the United States, and this can also be interwoven with geographical considerations when it comes to areas with lower socioeconomic status, high availability of substances, and less community cohesion. Exposure to chronic stress or trauma also increases risk of development of SUDs, as do factors arising from family and social influences, including modeling and observing parents, peers, partners, and community members who use alcohol or other substances.

The childhood and adolescent periods are crucial times for personality development and brain maturation. As such, family-based interventions have demonstrated success in decreasing substance use in adolescents by treating it in parents, increasing parental social support, and promoting alliance with providers. Public policy interventions operate on a broader scale with changes in taxes/prices for specific substances, raising legal drinking/smoking age, and increasing legal repercussions. Other types of interventions can be on an individual or group basis, delivered by a range of care providers, to address psychological, pharmacological, and social aspects [8].

Psychosocial interventions for SUDs target physical, behavioral, cognitive, emotional, interpersonal, and environmental factors to improve the overall functioning of the individual. Examples include psychotherapy (cognitive-behavioral therapy, contingency management, motivational interviewing, and brief interventions for alcohol and tobacco), community-based treatment, vocational rehabilitation, supportive housing, psychoeducation for family, peer support services, and integrated programs for individuals who have comorbid issues alongside their SUD. Psychosocial interventions can promote behavioral change and should be indispensable to any comprehensive SUD treatment program in alliance with medication-assisted treatment (MAT) [9].

Behavioral Changes from Relapse to Recovery

All human beings engaged in behavioral changes are confronted with feelings, thoughts, and actions regarding the maladaptive behaviors they are attempting to modify. In SUDs, learning and memory are reinforced via neurotransmitters such as dopamine, which are increased in circuits that result in biochemical changes that can impact thoughts and memories. This neurochemical process allows for people,

situations, and places to be imprinted on the brain and subsequently experienced as cues. These can be any stimuli (friends who use, emotions, sounds, places, or objects) that are associated with the substance use, and they can become strongly associated with the substance's effects [10]. Specifically, these cues take the form of *triggers*, which are defined as external or internal events that instigate thoughts or emotions related to substance use. When individuals are faced with various triggers, they may experience an *urge*, or an impulsive intention to use. The culmination of this progression is a *craving*, which is a very strong learned response with powerful motivating properties often resulting from specific memories (i.e., conditioned cues and triggers). Cravings are mediated by brain activation in the amygdala, and they are frequent in the early weeks or months after the individual decides to stop the substance. Fortunately, cravings can gradually decrease as RP strategies are assimilated.

Models of Relapse and Relapse Prevention

Relapse is a process that happens gradually. In each of the three stages below, there are warning signs and ways to prevent progression to the next stage. The goal of treatment is to prevent physical relapse.

Stage One: Emotional Relapse

During this stage, the individual has not started thinking about using substances and has not resumed use. However, the individual may be in denial or experiencing many negative emotions, which lead to strong cravings to use. Warning signs in this stage include negative emotions (anxiety, depression, anger, guilt, shame, embarrassment) and dysfunctional behaviors (isolation or social withdrawal, difficulties attending or engaging in therapy/support groups, poor self-care, refusal of others support or efforts). It is important for the individual to identify specific triggers and avoid certain people, location, situations, and emotions. This is a good time to learn coping/relaxation strategies, start positive lifestyle changes, and identify a reliable support network.

Stage Two: Mental Relapse

During this stage, there are conflicting desires between "wanting to use" and "not wanting to use." At this time, the individual's mind starts to rationalize any negative emotions from the previous stage that have not been resolved. Warning signs include increased cravings to use, romanticizing past use, minimizing consequences of use, reaching out to friends or acquaintances who are still using substances, lying behaviors, and planning to relapse. Consider reviewing negative consequences that the individual has identified previously and encourage the individual to share his/her thoughts without feeling embarrassed.

Stage Three: Physical Relapse

During this stage, the individual actively returns to substance use or other dysfunctional behaviors. This stage can be further divided into a *lapse*, that is, an initial use that is a slip or setback in abstinence, versus a full *relapse*, signifying a complete return to previous maladaptive behavior patterns that re-perpetuate the substance use. During this stage, the role of the clinician is to encourage the individual to return to RP plans developed from early stages and practice exit strategies. It is important to reflect on sequences of events preceding physical relapse, as this can be an opportunity to identify issues to process and correct in therapy. It is possible for an individual who has had a brief lapse to return to recovery practices and abstinence with proper support [11].

The Cognitive-Behavioral Framework of Relapse

The CBT framework, which is discussed in a separate chapter, posits that maladaptive cognitive distortions or beliefs are formed from previous experiences, and in turn influence a person's thoughts, feelings, and behaviors in future experiences. In individuals with SUDs, these cognitive distortions end up reinforcing the substance use as the only "solution" to a situation, precluding any consideration of other choices that could be made. Thus, when such an individual is faced with a trigger, the risk of developing cravings and returning to substance use is high. The cognitive-behavioral model of relapse was first conceptualized by G. Alan Marlatt and colleagues in 1985 and has remained one of the most influential models of relapse (Fig. 6.2). Marlatt's work was notable for first making the key distinction between lapse and relapse, as previous behavioral research had strictly defined a relapse as any return of the problem behavior, regardless of its duration or nature. Marlatt's original cognitive-behavioral model of relapse is shown in the figure below.

However, the interplay of the components of the model (including self-efficacy, expectations, and perceptions of the substance) and the intensity of the abstinence violation effect are affected by psychosocial context and are not necessarily sequential as depicted. This led Marlatt and Witkiewitz to propose a revised, more dynamic CBT model of relapse, which accounts for more static risk factors such as family history, comorbid psychiatric conditions, and social support or lack thereof, alongside contextual cues and the proximal or immediate risks presented by the specific high-risk situation [12]. The revised model also serves to highlight more points of intervention for RP techniques, including identifying warning signs and high-risk situations, building a social network for recovery, challenging personal cognitive distortions, appropriate transitioning through levels of care, and developing strategies to improve treatment adherence.

In recent years, the concept of "mindfulness" – which entails an active attentiveness to experiencing the present moment, and accepting it as it is – is included in substance use treatment. Mindfulness-based relapsed prevention, or MBRP, integrates mindfulness-based meditation practices into traditional psychotherapy for

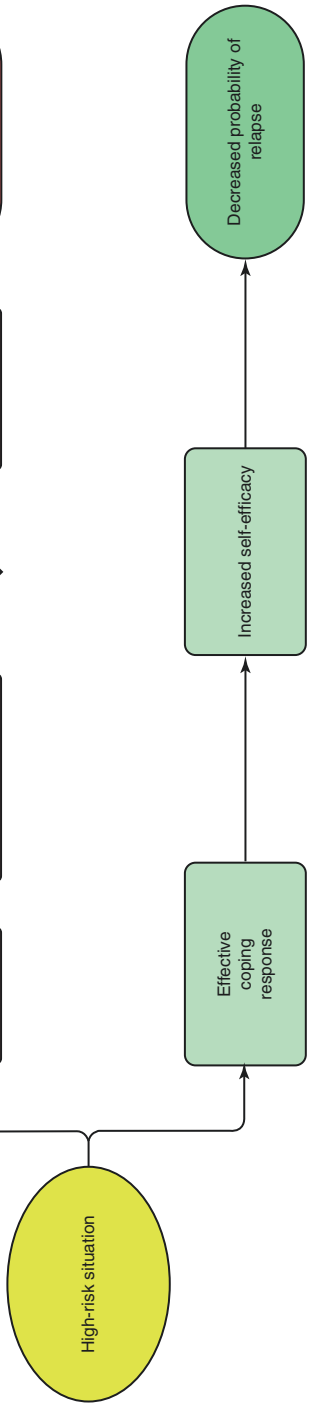

Fig. 6.2 Cognitive-behavioral model of relapse [12]

RP. The goal of mindfulness-based meditation in this context is to help patients better tolerate psychological discomforts, such as those accompanying cravings or withdrawal symptoms, that might otherwise lead to a relapse [13].

Conclusion

In this chapter, we have provided key definitions for relapse and recovery, but it is important to emphasize that these processes are multifaceted and individualized. We have identified the biopsychosocial factors that affect the risk of relapse as well as the trajectory of recovery and have described means of monitoring and measuring progress in SUD treatment. As our understanding of SUDs has expanded over time, more treatment modalities have become available in the realms of medical management, psychotherapeutic interventions, and interdisciplinary collaboration.

Review Questions

1. A 50-year-old patient you see in your outpatient practice who was using methamphetamines had been able to stop her use for 2 months while trying to return to work. For the past two weekends in a row, the patient reports use of methamphetamines on Friday and Saturday. You sit down with your patient to discuss a recent relapse. You start by identifying "triggers," which involve which of the following?
   A. Feelings, thoughts, and emotions
   B. Ideals, psychologies, and therapies
   C. People, places, and things
   D. Coping strategies
   E. People, places, things, feelings, thoughts, and emotions

   Correct Answer: E

   Triggers are internal and external cues that cause a person in recovery to crave drugs and eventually relapse. External triggers are people, places, activities, and objects that elicit thoughts or cravings associated with substance use. Individuals in recovery can stay away from the dangers of external triggers by developing action plans to avoid triggers that remind them of past drug use. Internal triggers are more challenging to manage than external triggers. They involve feelings, thoughts, and emotions formerly associated with substance abuse.

   B. Ideals, psychologies, and therapies are not triggers. Humanistic and existential approaches (including empathy, encouragement of affect, reflective listening, and acceptance of the individual's subjective experience) are useful in any type of brief therapy session, whether it involves psychodynamic, strategic, or cognitive-behavioral therapy. They help establish rapport and provide grounds for meaningful engagement with all aspects of the treatment process.

   D. Coping strategies provide a substitute or alternative that leads to healthier ways of dealing with triggers.

Reference: Daley DC, Marlatt GA. Overcoming your alcohol or drug problem: effective recovery strategies: therapist guide. 2nd ed. Oxford: Oxford University Press; 2006.

2. You have a patient in your outpatient practice who quit alcohol and opioids 3 weeks ago after naltrexone was started, but the patient is struggling with managing his emotions and stress related to his work and his wife. The patient worries about relapsing due to not being able to handle high-risk situations. You feel he would benefit from a group environment where he could learn techniques to manage his cravings as well as work on his interpersonal skills. One thing you know about the patient is his readiness to learn and practice what it is discussed. Which of the following groups would be most appropriate for you to refer him to?
   A. Milieu group
   B. Psychoeducational recovery group
   C. Coping skills group
   D. Counseling group
   E. Specialized group

Correct Answer: C

Skill groups are aimed at helping patients develop or improve their intrapersonal and interpersonal skills. For example, these groups teach problem-solving methods and stress management, cognitive, and relapse prevention strategies. Relapse prevention strategies help patients identify and manage early signs of relapse (the relapse "process"), identify and manage high-risk factors, or learn steps to take to intervene in a lapse or relapse.

A. Milieu groups are offered in residential and hospital programs and usually involve a group meeting to start and/or end the day. A morning group may review the upcoming day's schedule, whereas an evening group may review the day's treatment and recovery activities and allow participants to reflect on their experiences that day.

B. Psychoeducational recovery groups provide information about specific topics related to addiction and recovery and help patients begin to learn how to cope with the challenges of recovery. These groups use a combination of lectures, discussions, educational videos, behavioral rehearsals, and completion of written assignments such as a recovery workbook or personal journal.

D. Counseling groups (also called therapy groups, problem-solving groups, or process groups) are less structured and give the participants an opportunity to create their own agenda in terms of problems, conflicts, or struggles to work on during group sessions. These groups focus more on gaining insight and raising self-awareness than on education or skill development.

E. Specialized groups may be based on developmental stage (adolescents, young adults, adults, older adults), gender, different clinical populations (pregnant women or women with small children addicted to opioids, or anyone involved in the criminal justice system), or groups addressing specific issues or populations (parenting issues, anger or mood management, or trauma).

Reference: Group therapies. In: Ries RK, editor. The ASAM principles of addiction medicine. 5th ed. Philadelphia: Wolters Kluwer Health; 2014. p. 847–8.

3. A 28-year-old patient got referred by her primary care clinician to you as the addiction expert. When you call the patient, she expresses mixed feelings about attending your appointment because she wants to quit someday but not now. You start by identifying the stages of change. In which stage is the one more likely the patient to be?
   A. Relapse
   B. Precontemplation
   C. Contemplation
   D. Preparation
   E. Action

   Correct Answer: C

   The patient is ambivalent about when to start her treatment. She is contemplating a change but has not yet developed a plan for it or taken action to attend the program recommended by her physician.

   A. Relapse is not the patient's stage of change. It is only after several relapses that the person discovers what recovery from an addiction means.

   B. Precontemplation is the stage where the person does not see their SUD as significant as compared to the benefits. Characteristics of this stage are a lack of interest in change, and having no plan or intention to change. We might describe this person as unaware.

   D. Preparation is a stage where the person accepts responsibility to change her or his behavior. She evaluates and selects techniques for behavioral change. Characteristics of this stage include developing a plan to make the needed changes, building confidence and commitment to change, and having the intention to change within a period of time. We might describe this person as willing to change and anticipating the benefits of change.

   E. Action is a stage where the person engages in self-directed behavioral efforts to change while gaining new insights and developing new skills. Although these efforts are self-directed, outside help may be sought. This might include rehab or therapy. Characteristics of this stage include consciously choosing new behavior, learning to overcome the tendencies toward unwanted behavior, and engaging in change actions. We might describe this person as enthusiastically embracing change and gaining momentum.

   Reference: Miller WR, Rollnick S. Motivational interviewing: helping people change. 3rd ed. New York: Guilford Press; 2013.

4. A 45-year-old man stopped his buprenorphine treatment a year ago after 10 years of full abstinence. The patient was actively involved in your program where he was attending CBT/SUD groups weekly and monthly follow ups with you. After 6 months the patient came back to you describing intense desire to use opioids after he started to work in a rehab program where he started to perceive substance availability if he asked a person he knows from the past. The patient started to notice an intense desire to use opioids again

with an increased likelihood of seeking this substance by planning to find the person and ask where to go and use. Which patient characteristic best defines this experience?

A. Withdrawal
B. Urge
C. Triggers
D. Drug craving
E. Conditioned positive reinforcement

Correct Answer: D

Drug cravings are a longing for or desire to use a substance, varying in intensity from mild to very strong. Cravings can be a desire for the euphoric effects of the substance, or a means to avoid or escape unpleasant emotions or physical symptoms such as those associated with withdrawal.

A. Withdrawal: A group of symptoms of variable clustering and degree of severity which occur on cessation or reduction of use of a psychoactive substance that has been taken repeatedly, usually for a prolonged period and/or in high doses. The syndrome may be accompanied by signs of physiological disturbance. A withdrawal syndrome is one of the indicators of a dependence syndrome. It is also the defining characteristic of the narrower psycho-pharmacological meaning of dependence.

B. Urge: An urge is an intention to use a substance once the individual is experiencing cravings. There can be a strong craving with very little intention to use, or the intention to use can be quite high, making the individual more vulnerable to relapse unless the person then utilizes active coping strategies to manage these cravings and urges.

C. Triggers: Triggers are external or internal events that instigate thoughts or emotions related with the substance use process. Triggers often induce cravings. The goal of identifying the trigger is to learn management of external factors (people, places, events, experiences, or objects) or internal (feelings or thoughts).

E. Conditioned positive reinforcement: This involves the addition of a reinforcing stimulus following a behavior that makes it more likely that the behavior will occur again in the future. When a favorable outcome, event, or reward occurs after an action, that particular response or behavior will be strengthened.

Reference: Koob GF, Moal ML. Neurobiology of addiction. London: Elsevier AP; 2011.

5. A 33-year-old woman who is in recovery attended for the first time a party after completing 8 months of sobriety. She was offered not once but twice an alcoholic beverage by a stranger. On the third occasion when the same person offered her the drink she briefly and kindly said: “I have a medical problem and I cannot drink. Could you please not offer me a drink again?”. The patient moved to another section of the party where she knew sober friends were socializing.

According to the original cognitive-behavioral model of relapse, which of the following helped her to decrease the chance of relapse?

A. Ineffective coping response
B. Positive outcome expectancy
C. Increased self-efficacy
D. Abstinence violation effect
E. High-risk situation

Correct Answer: C

Explanation: The original CBT model of relapse begins with the individual presented with a high-risk situation (E), defined as a situation in which the individual's attempt to refrain from substance use is challenged. The individual may then respond with either an ineffective coping response (A) or an effective coping response. An individual who utilizes an ineffective coping response will tend to cave to a temptation or pressure, possibly carried along by their positive outcome expectancies (B) of the initial effects of using the substance. This leads to the initial use, or lapse. The lapse can be followed by the abstinence violation effect (D), in which the individual experiences guilt and demotivation, focusing excessively on blaming themselves for their failure, to the detriment of their previous commitment to sobriety ("why even bother anymore, when I've already messed up"). The end result of all of these steps is an overall increased likelihood of relapse. The only response that does not follow this is C, increased self-efficacy, which is achieved when the individual is able to exercise an effective coping response, that is., successfully enact their relapse prevention plan to remove themselves from the high-risk situation or otherwise refrain from lapse. The successful maintenance of abstinence reinforces the individual's confidence that they will succeed again in similar situations, and their risk of relapse is lowered.

Reference: Witkiewitz K, Marlatt GA. Relapse prevention for alcohol and drug problems: that was Zen, this is Tao. Am Psychol. 2004;59(4):224–35.

6. Which of the following is an example of an individual in the preparation stage of the transtheoretical model of change?
   A. Mrs. A has enjoyed smoking cigarettes for years while socializing with her friends but is thinking about cutting down now that she is expecting a grandchild.
   B. Mr. B smokes marijuana daily and is adamant that it is the only thing keeping his anxiety under control. He denies any negative impacts on his mental or physical health, and sees no reason to stop.
   C. Mr. C has not used methamphetamine for 2 years now. He is proud of how he has "rebuilt" his life and is wary of returning to any kind of drug use.
   D. Ms. D has deleted her drug dealer's contact information from her phone and has been going to the gym weekly to get her out of the house where she otherwise used to use heroin alone.
   E. Mr. E has resolved to go to his first AA meeting this coming week, after a recent scare in which he almost got into a car accident while driving "buzzed."

   Correct Answer: E

Explanation: Mr. E has made a plan that he intends to act upon within the next 30 days and has come to a realization about how his drinking is jeopardizing himself and others.

A is an example of the contemplation stage. B is in the precontemplation stage. C is in the maintenance stage. D is in the action stage.

Reference: Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. Am J Health Promot. 1997;12(1):38–48.

References

1. Daley DC, Marlatt GA. Overcoming your alcohol or drug problem: effective recovery strategies: therapist guide. 2nd ed. Oxford: Oxford University Press; 2006. p. 181–93.
2. Gumbley SJ. Recovery in the 21st century. J Addict Nurs. 2016;27(2):143–7.
3. Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. Am J Health Promot. 1997;12(1):38–48.
4. Gudin JA, Mogali S, Jones JD, Comer SD. Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. Postgrad Med. 2013;125(4):115–30.
5. Betty Ford Institute Consensus Panel. What is recovery? A working definition from the Betty Ford Institute. J Subst Abus Treat. 2007;33(3):221–8.
6. White WL. Addiction recovery: its definition and conceptual boundaries. J Subst Abus Treat. 2007;33(3):229–41.
7. Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW. A meta-analytic review of psychosocial interventions for substance use disorders. Am J Psychiatry. 2008;165(2):179–87.
8. Stone AL, Becker LG, Huber AM, Catalano RF. Review of risk and protective factors of substance use and problem use in emerging adulthood. Addict Behav. 2012;37(7):747–75.
9. Drake RE, O'Neal EL, Wallach MA. A systematic review of psychosocial research on psychosocial interventions for people with co-occurring severe mental and substance use disorders. J Subst Abus Treat. 2008;34(1):123–38.
10. Center for Substance Abuse Treatment. Chapter 2: How stimulants affect. In: Treatment for stimulant use disorder. Treatment improvement protocols (TIP) series no. 33. Rockville: Substance Abuse and Mental Health Services Administration; 2001. p. 13–33.
11. Melemis SM. Relapse prevent and the five rules of recovery. Yale J Biol Med. 2015;88(3):325–32.
12. Witkiewitz K, Marlatt GA. Relapse prevention for alcohol and drug problems: that was Zen, this is Tao. Am Psychol. 2004;59(4):224–35.
13. Grant S, Colaiaco B, Motala A, Shanman R, Booth M, Sorbero M, et al. Mindfulness-based relapse prevention for substance use disorders: a systematic review and meta-analysis. J Addict Med. 2017;11(5):386–96.

Part II

Addictions and Their Treatments

Nicotine

7

Stephanie L. Hsia, Anna K. Mischel, and Arthur L. Brody

High-Yield Review Points

- Tobacco use continues to be the leading preventable cause of morbidity and mortality in the United States.
- Nicotine is a nicotinic receptor agonist which produces stimulant effects, reduces anxiety, and stimulates the dopamine reward pathway through release of several neurotransmitters.
- The combination of behavioral and pharmacological treatment for tobacco use disorder is more effective than either intervention alone.
- Cognitive behavioral therapy in individual and group settings is a first-line behavioral treatment for tobacco use disorder.
- Combination nicotine replacement therapy, bupropion SR, and varenicline are first-line pharmacotherapies for tobacco use disorder.

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Introduction

Epidemiology

The prevalence of tobacco dependence has been steadily declining since the Surgeon General's report in 1964 that linked smoking with lung cancer. The rate of smoking in the United States has dropped from 42% in 1964 to 14% (34.3 million) in 2017. Certain subpopulations are at a higher risk for smoking than others. In 2016, the prevalence of cigarette smoking was greater in individuals who were male, aged 24–65, American Indian, Alaska native, or multiracial, uninsured or insured by Medicaid, had a General Education Development (GED) Certificate, identified as lesbian, gay, or bisexual, living below the poverty line, lived in the Midwest or South, or had a disability [1]. Additionally, individuals with mental illnesses (e.g., schizophrenia, mood and anxiety disorders, and substance use disorders) have elevated rates of smoking compared to the general population. In fact, people with mental illness and/or substance use disorder consume 40% of cigarettes sold in the United States [2].

Consequences of Use

According to the Surgeon General Report, smoking is the leading preventable cause of morbidity and mortality in the United States, resulting in 480,000 deaths annually [3]. Smoking damages nearly every organ in the body, with the most common severe medical complications being cancer, respiratory diseases, cardiovascular disease, diabetes, immune and autoimmune disorders, eye disease, and reproductive and developmental effects [3]. On average, cigarette smokers die 10 years earlier than people who have never smoked [4]. In addition, primary and secondhand smoke expose people to more than 7000 chemicals, some of which are carcinogenic. Smoking costs the United States $300 billion per year with more than $170 billion for medical care and another $165 billion lost in productivity due to premature death [5]. Given these detrimental effects of cigarettes on both individual health and society, it is vital to better understand tobacco, tobacco-related products, and tobacco use disorder in greater detail.

Pharmacology

Pharmacokinetics

Nicotine is a weak base ($pK_a = 8.0$), which requires a slightly alkaline pH to absorb across physiological membranes and into the circulation. The two primary routes of delivery of nicotine from tobacco are inhalation and buccal. In cigarettes, pipes, and cigars, tar droplets produced from the burning of tobacco deliver nicotine directly to the lungs. Since inhalation bypasses first pass metabolism, nicotine is rapidly

absorbed into the circulation and reaches high concentrations in the brain within 10–20 seconds. On average, smoking one cigarette delivers approximately 1 mg of nicotine. In chewing tobacco, snuff, and nicotine gum/lozenges, nicotine is buffered in a slightly alkaline pH which facilitates absorption through buccal membranes. Compared to inhalation, buccal absorption is slower, and nicotine concentrations in the brain increase more gradually, reaching peak concentrations in 30 minutes. Nicotine is also readily absorbed through the skin, though at a slower rate than buccal and inhaled administration. After absorption, nicotine readily distributes through bodily tissues and is metabolized by CYP2A6 in the liver to its primary metabolite, cotinine. Cotinine is partially excreted unchanged by the kidney and metabolized to further metabolites which are then eliminated. Cigarette smoke is an inducer of CYP1A2 and, therefore, may affect plasma levels of drugs metabolized through this enzyme [6].

Pharmacodynamics

Nicotine is a nicotinic acetylcholinergic receptor (nAChR) agonist. When nicotine activates the nAChR, it facilitates the release of several neurotransmitters, including dopamine, norepinephrine, acetylcholine, serotonin, glutamate, γ-aminobutyric acid (GABA), and endorphins. These neurotransmitters are responsible for the physiological and addictive effects of nicotine. The release of norepinephrine and acetylcholine leads to its stimulant effects, namely, increases in heart rate and blood pressure and appetite suppression. The release of GABA and endorphins leads to reduction of anxiety and tension. Chronic administration of nicotine causes the release of dopamine in the mesolimbic area, corpus striatum, and prefrontal cortex, and neuroadaptive changes occur which form the pharmacological basis of nicotine addiction. With chronic administration, the number of nicotinic acetylcholinergic receptors in the brain increases, leading to tolerance and withdrawal symptoms [7].

Pathogenesis

Intoxication

As the doses of nicotine found in most commercially available products are quite low, nicotine intoxication is rarely seen. However, nicotine toxicity has been reported with oral ingestion of liquid nicotine that is used for electronic cigarettes as these liquids can contain lethal doses of nicotine if ingested inappropriately [8, 9]. At commercially available doses, nicotine administration produces stimulant effects, such as increased heart rate and blood pressure, arousal, and reduction of anxiety. At high doses, nicotine can produce bradycardia, hypotension, and depressed mental status due to ganglionic blockade [7]. Symptoms of nicotine overdose can develop within 15–90 minutes of exposure and include gastrointestinal upset, nausea, vomiting, respiratory depression, and seizures. Treatment of nicotine

intoxication occurs primarily in cases of poisoning or overdose. Primary treatment consists of activated charcoal to remove nicotine from the gastrointestinal tract and supportive treatments and care (e.g., benzodiazepines for seizures, fluids/vasopressors for hypotension) [10].

Withdrawal

Nicotine withdrawal symptoms can occur as early as 30–40 minutes after smoking a cigarette. The rapid onset of withdrawal symptoms and desire to alleviate them is one of the primary reasons people use tobacco and why nicotine has such addictive potential [7]. Common symptoms of nicotine withdrawal are irritability, restlessness, anxiety, difficulty concentrating, increased appetite, insomnia, and depressed mood [11]. Withdrawal symptoms typically peak within 2–3 days after quitting, and last 2–4 weeks, but may persist for months in some individuals. Effective treatments for nicotine withdrawal include first-line therapies for tobacco use disorder: nicotine replacement therapy, bupropion, and varenicline [12]. These pharmacological options are discussed in further detail below.

Tobacco Use Disorder

Diagnosis

Diagnostic criteria for tobacco use disorder (TUD), as defined in the *Diagnostic and Statistical Manual for Mental Disorders, fifth edition* (DSM-5), is similar to that of other substance use disorders (i.e., tolerance, withdrawal, criteria about problems resulting from use) [11]. A diagnosis of TUD is common among individuals who use tobacco daily, but uncommon among those who do not use tobacco daily or who solely use nicotine-containing products. Tolerance to tobacco is often indicated by the absence of dizziness and/or nausea after tobacco intake. Substance use diagnostic criteria that are uncommon in TUD include spending excessive time obtaining tobacco (as it is readily and legally available), spending time recovering from tobacco (since intoxication is rare), and recurrent tobacco use resulting in failure to fulfill major role obligations. The presence of these criteria may indicate more severe TUD [11].

Assessment

The first step in treating TUD is to screen for and assess an individual's tobacco use. The 5 As and "Ask, Advise, Refer" are two useful frameworks for brief smoking cessation interventions. The 5As consist of five steps: (1) Ask every patient about their smoking status; (2) Advise the patient to quit; (3) Assess the patient's readiness to quit; (4) Assist the patient with their quit attempt if they are ready; and (5) Arrange

Table 7.1 Heaviness of smoking index for nicotine dependence [14]

	Response	Point value
Items		
How soon after waking do you smoke your first cigarette?	<5 min	3 points
	5–30 min	2 points
	31–60 min	1 point
	>60 min	0 points
How many cigarettes do you smoke each day?	>30 cigarettes	3 points
	21–30 cigarettes	2 points
	11–20 cigarettes	1 point
	≤10 cigarettes	0 points
Scoring		
Nicotine dependence score	0 points	No dependence
	1–2 points	Low dependence
	3–4 points	Moderate dependence
	5–6 points	High dependence

for follow-up. "Ask, Advise, Refer" consists of three steps: (1) Ask the patient about their smoking status; (2) Advise the patient to quit; and (3) Refer the patient to evidence-based smoking cessation strategies [12, 13].

Appropriate assessment of a patient's tobacco use is an integral component of treating TUD. To help guide treatment, the patient's level of nicotine dependence should be determined. One brief and validated scale which may be used to assess a patient's nicotine dependence is the Heaviness of Smoking Index (HSI), an abbreviated version of the Fagerström Test for Nicotine Dependence [14]. The HSI (Table 7.1) assesses a patient's dependence based on their time to first cigarette and total daily cigarette intake. Of note, one pack contains 20 cigarettes.

Treatment of Tobacco Use Disorder

Overview of Treatment

Once an individual's nicotine dependence has been assessed, treatment should be initiated. If the individual is ready and willing to attempt to quit, the provider should work with him/her to plan for and set a quit date—the day the individual stops all tobacco. Since nicotine addiction includes behavioral and physiological dependence, treatment of TUD should involve behavioral as well as pharmacological interventions. The combination of medication and counseling has been shown to be more effective in helping patients remain tobacco-free compared to either intervention alone [12]. Though cigarette smoking is the most common form of tobacco use, it is also important to ask and assist individuals who use non-cigarette tobacco products [15]. Electronic cigarettes in particular have become more frequently used and are discussed in more detail below. Behavioral

interventions should be recommended for all tobacco users; however, evidence-based recommendations for pharmacological treatment of non-cigarette tobacco users are limited [16].

Nonpharmacological Treatment

Psychotherapy is a commonly used first-line treatment for TUD. Both individual and group therapy are effective for treating TUD and are associated with abstinence rates of about 20–25% [12, 17, 18]. Among many psychotherapies that are used for TUD, cognitive-behavioral therapy (CBT) adapted for smoking cessation is the most widely studied and used technique [12]. CBT typically includes (1) education about smoking addiction, withdrawal, and relapse; (2) recognizing danger situations (triggers) that could lead to relapse; (3) developing coping skills, such as avoiding temptation, coping with negative affective states, reducing overall stress, and distracting attention from smoking urges with other activities (i.e., relapse prevention techniques); (4) social support (both within and outside of treatment); and (5) encouragement to taper off all tobacco products. At each session, CBT and other psychotherapies usually include questioning about recent cigarette usage and monitoring of exhaled carbon monoxide (CO) levels, with levels of ≤4 parts per million (ppm) being consistent with no cigarette usage within the past 24 hours [19]. CBT (and other psychotherapies) can be done in group or individual format.

During psychotherapy for smoking cessation and in other settings with tobacco users who are not yet ready to try quitting, motivational interviewing (MI) techniques are often used. These techniques are designed to encourage patient engagement in active behavior change and include, but are not limited to, exploring self-ratings of importance of quitting and confidence in quitting using open-ended questions and reflection. MI can include the "5 Rs," which consist of determining "Relevance" of quitting to the tobacco user, discussing "Risks" of continued tobacco use, exploring "Rewards" of quitting, examining "Roadblocks" to quitting, and "Repetition" of the tobacco cessation discussion [20]. MI has consistently been found to increase numbers of quit attempts and to be effective for engaging smokers with mental illness.

In addition to in-person therapies, Internet-based, mobile phone text message-based, printed self-help, and telephone-based interventions have been shown to be more effective than non-active control conditions in helping smokers achieve abstinence. Much ongoing research is focused on improving delivery of these treatments and tailoring treatments to specific subgroups of smokers (e.g., smokers with mental illness) [21].

Pharmacological Treatment

FDA-approved treatments for TUD are nicotine replacement therapy (NRT), bupropion, and varenicline. All three treatments are recommended by the guidelines as first-line pharmacological options for TUD. Meta-analysis has suggested that both

combination NRT and varenicline may be more effective than bupropion or NRT monotherapy [22]. Selection of an agent should be based on patient-specific characteristics [12, 13].

Nicotine Replacement Therapy

Nicotine replacement therapy (NRT) is a first-line recommended treatment for TUD. NRT's primary mechanism of action is as a nicotinic agonist at nAChR [7]. Since the absorption of nicotine from NRTs is much slower than that of cigarettes, NRTs carry a minimal risk of dependence/addiction while still achieving sufficient concentrations to relieve withdrawal symptoms. NRTs do not produce the peak in concentration and subsequent "rush" that smokers get from rapid absorption of nicotine through cigarettes, thereby reducing positive reinforcement from nicotine [7]. NRT can be categorized into two groups: long-acting and short-acting. The only currently FDA-approved long-acting form of NRT is the transdermal nicotine patch. The nicotine patch provides a steady amount of nicotine throughout the day and reduces nicotine dependence by relieving background cravings and reducing withdrawal [23]. The nicotine patch is typically administered once daily (approximately every 24 hours), though some remove the patch at bedtime to prevent side effects such as intense dreams. There are several forms of short-acting NRT: nicotine gum, lozenge, nasal spray, and oral inhaler. While the nicotine patch relieves background cravings, short-acting NRT relives breakthrough cravings and provides sensory stimulation (e.g., hand-to-mouth motion) [23]. The different formulations of short-acting NRT primarily differ in their method of use and pharmacokinetics. Of the four forms, the nicotine nasal spray has the fastest absorption and, therefore, has the highest risk of perpetuating physiological dependence. Similarly, the nicotine inhaler most closely resembles a cigarette in terms of appearance and use and may perpetuate behavioral smoking habits. Therefore, the nasal spray and inhaler are not typically used as first-line options, but may be preferred in certain patients who are unable to use oral NRT [23].

Combination NRT

Studies have shown that combination NRT (use of a long-acting with a short-acting formulation) is more effective than monotherapy NRT. The use of long- and short-acting formulations together provides relief of both background and breakthrough cravings without increasing incidence of adverse effects [12, 20]. Though combination NRT is recommended as first-line therapy, there is no official dosing recommendation, and the dosing used in studies has varied [23]. The initial nicotine patch dose should be based on the patient's nicotine dependence (Table 7.2). Most patients can initially be started on the 2 mg dose of short-acting NRT (e.g., gum or lozenge), though patients who are highly dependent or who smoke less than 30 minutes after waking may be started on the 4 mg dose (Table 7.2). As general

Table 7.2 Package insert and guideline dosing recommendations for combination NRT[a]

	Nicotine Patch Strength	Nicotine Gum/Lozenge Strength
High dependence	21 mg/day × 6 weeks 14 mg/day × 2 weeks 7 mg/day × 2 weeks	Smokes <30 min after waking: 4 mg Smokes ≥30 min after waking: 2 mg 1 piece q1–2 hours prn cravings × 6 weeks 1 piece q2–4 hours prn cravings × 2 weeks 1 piece q4–8 hours prn cravings × 2 weeks
Moderate dependence	21 mg/day × 6 weeks 14 mg/day × 2 weeks 7 mg/day × 2 weeks	2 mg strength 1 piece q1–2 hours prn cravings × 6 weeks 1 piece q2–4 hours prn cravings × 2 weeks 1 piece q4–8 hours prn cravings × 2 weeks
Low dependence	14 mg/day × 6 weeks 7 mg/day × 2 weeks	2 mg strength 1 piece q1–2 hours prn cravings × 6 weeks 1 piece q2–4 hours prn cravings × 2 weeks 1 piece q4–8 hours prn cravings × 2 weeks

[a]Dosing from package insert recommendations, tapering schedule should still be individualized to each patient and extended if clinically indicated

guidance for tapering, patients may remain on their initial dose of the nicotine patch for 6 weeks, and then step down to the next patch for 2 weeks [24]. It is important to realize that package insert tapering recommendations should only serve as general guidance and that tapering of NRT should be individualized and based on the patient's progress (e.g., a patient should not step down to the next patch strength if s/he is still experiencing significant cravings or had a recent slip). NRT has been studied in extended treatment for up to 6 months; therefore, extending NRT treatment past the recommended 10 weeks is safe [12]. The recommended maximum daily dosages of the gum and lozenge are 24 pieces and 20 pieces, respectively [25]. Initially, it may be beneficial for patients to use at least 6 pieces of short-acting NRT daily as cravings are typically strongest within the first few weeks after quitting [23].

Common adverse effects with NRT are similar to that of nicotine and include increased heart rate, blood pressure, headache, stomach upset (if incorrectly swallowed), insomnia, and nervousness. For the nicotine patch, patients may experience irritation or redness at the application site, or, uncommonly, allergic reactions. If a patient has any signs of an allergic reaction (edema, hives, shortness of breath), s/he should discontinue use immediately [24, 25]. NRT has been shown to be safe to use in patients with cardiovascular disease. Caution should be exercised when using NRT in patients with a recent (<2 weeks) myocardial infarction, serious arrhythmias, or serious angina. However, it is also important to note that NRT is, in general, still safer than cigarette smoking in these at-risk patients [12].

Counseling on how to properly use NRT is crucial to its efficacy. For the nicotine patch, patients should be instructed to apply the patch to a clean, dry, patch of skin on the chest, back, stomach, or upper arm. They should wash their hands after application and rotate application sites daily to minimize skin irritation. Patches should only be worn for a maximum of 24 hours, though if the patient experiences abnormal dreams or has difficulty sleeping s/he may remove the patch before bedtime. Patches should be properly disposed of out of reach of children or animals [24].

For the nicotine gum, patients should be instructed on the "chew and park" method. Patients should be instructed to chew the gum until they experience a tingling sensation or peppery taste in their mouth. Once they do, they should "park" the piece of gum between their gum and cheek (as this is where the nicotine absorbs). After the tingling/taste stops, they should repeat, but "park" the piece in a different area between their gum and cheek. They should repeat this process until the tingle/taste no longer occurs (approximately 30 minutes per piece of gum) [25].

For the nicotine lozenge, patients should be instructed to suck on the lozenge and let it dissolve in their mouth gradually over 30 minutes. They should move the lozenge to different sides and areas of their mouth to minimize skin irritation. They should not chew the lozenge as this may affect nicotine release and cause irritation. For both the gum and lozenge, patients should also be instructed to avoid eating or drinking at least 15 minutes before or after or during use of the gum since it requires physiological pH to absorb. Patients should also be instructed not to swallow the nicotine gum or lozenge as doing so may cause significant stomach upset.

Bupropion (Zyban®)

Bupropion SR (Zyban®) is an antidepressant which is FDA-approved for treatment of TUD. Its proposed mechanisms of action are the inhibition of dopamine and norepinephrine reuptake and antagonism of nAChR [12]. Bupropion should be initiated 1–2 weeks before the target quit date. The dosing for TUD is 150 mg daily for 3 days, and then increase to 150 mg twice daily for 7–12 weeks [12]. Bupropion is contraindicated in patients at risk for seizure (i.e., with history of seizure or eating disorders) and in patients who have taken a monoamine oxidase inhibitor (MAOI) in the past 14 days. Since bupropion is an antidepressant and can have effects on mood, its psychiatric effects should be considered when being used in the psychiatric population. Common adverse effects of bupropion include insomnia, dry mouth, increased blood pressure, and weight loss. Bupropion is a strong CYP2D6 inhibitor and is extensively metabolized in the liver. Therefore, drug–drug interactions should be considered, and dose reduction may be required in patients with hepatic dysfunction [26].

Varenicline (Chantix®)

Varenicline (Chantix®) is a partial α_4 β_2 nicotinic acetylcholine receptor agonist. It prevents nicotine withdrawal and cravings by partially stimulating the nicotine receptor to a degree lower than that of cigarettes and below the threshold for the dopamine reward pathway responsible for addiction. Varenicline should be initiated 1 week before the target quit date. The dosing for varenicline is 0.5 mg once daily for 3 days, then 0.5 mg twice daily for 4 days, then 1 mg twice daily for 3 months. Serious neuropsychiatric adverse effects (suicidal ideation, depression, aggression, changes in behavior) have been reported with use of

varenicline. Therefore, patients should be monitored for changes in mood/behavior, and caution should be exercised in psychiatric patients. The FDA removed the black box warning regarding neuropsychiatric events after a study demonstrated that use of varenicline in stable psychiatric patients (defined as clinically stable and receiving treatment for 6 months) was not associated with an increased incidence of neuropsychiatric events [27]. Other significant warnings include an increased risk of seizure and increased effect of alcohol. Patients should be educated to reduce the amount of alcohol they consume until they know how varenicline affects them. The most common adverse effect with varenicline is nausea, which can be minimized if the medication is taken after meals on a full stomach. Other common side effects include insomnia and abnormal dreams. Varenicline is primarily eliminated by the kidneys and, therefore, requires dose adjustment in patients with renal dysfunction [28].

Off-Label Treatments

Clonidine and nortriptyline have also been studied and shown some effectiveness for TUD. However, there are significant adverse effects associated with the use of these medications and variable dosing in studies for TUD. Therefore, clonidine and nortriptyline are only recommended as second-line treatment options for patients who have failed or are not candidates for first-line pharmacotherapy options [12].

Electronic Cigarettes/Vaping

Background and Formulations

Electronic cigarettes, often called "e-cigs," "e-hookahs," "mods," "vape pens," "vapes," "tank systems," or "electronic nicotine delivery devices" are small inhalers that simulate cigarette smoking by producing an aerosol that is inhaled [29]. Typical e-cigarettes use a battery-powered heating coil to aerosolize a liquid solution known as e-liquid or "eJuice." These e-liquids usually contain a mixture of nicotine, flavor, and diluent (typically propylene glycol and/or vegetable glycerin) [30]. E-liquids can be offered in several different strengths of nicotine. For example, one e-cigarette brand offers pods that contain either 3% (23 mg) or 5% (40 mg) nicotine by weight. Electromechanically, current e-cigarette technology employs a coil of resistive wire around a wick material positioned across the axis of a narrow flow tube through which the user draws in a mouthful of aerosol. E-cigarette usage leads to peak plasma nicotine concentrations similar to conventional cigarette usage making it a possible alternative [31].

The use of e-cigarettes has rapidly proliferated worldwide, with a rise in adjusted national sales from $11.6 million in 2010 to $751.2 million in 2016 [32]. While smoking cessation and harm reduction are a primary reason people report using

e-cigarettes, almost 1/3 of users are nonsmokers who initiate nicotine usage with e-cigarettes [33, 34]. Because e-cigarettes do not contain tobacco, they appear to be less harmful than conventional cigarettes which deliver thousands of chemicals. Harmful chemicals and particulate matter in e-cigs are ~9–450 times lower of those found in conventional cigarettes, and similar to levels found in the FDA-approved nicotine inhaler [35, 36]. Currently, e-cigarettes are not approved by the US Food and Drug Administration for the treatment of tobacco use disorder.

Current Evidence

Despite the growing popularity of e-cigarettes, research on their efficacy as an aid for smoking cessation is not unanimous. One review of relevant studies found evidence of long-term smoking cessation with e-cigarette use without any major adverse events [37]. Included in this review were two randomized control trials that found that using e-cigarettes with nicotine increased the likelihood of smoking cessation when compared with nicotine-free e-cigarettes. Another review analyzed relevant studies published between 2003 and 2017 and found that e-cigarettes were moderately effective with regard to smoking reduction (48–59%) and cessation (13–23%), with frequent reports of non-severe adverse events that diminished with time (i.e., throat irritation, anxiety, and insomnia) [38]. Overall, the literature points toward cautious optimism for smoking reduction; however, more evidence is needed to fully understand if and how e-cigarettes facilitate smoking cessation.

Risks/Disadvantages

Significant concerns have been raised about dependence on nicotine delivered by the introduction of e-cigarettes into the marketplace. Usage by young adults and adolescents is on the rise, which raises concern that e-cigarettes function as a gateway to nicotine and/or tobacco dependence. In a study of US high school juniors and seniors, students who used e-cigarettes were 6 times more likely to initiate conventional cigarette use during a 16-month follow-up period, and 40% of them did so, indicating that e-cigarette usage may lead to nicotine dependence [33, 39, 40].

In addition, many e-cigarette users have trouble weaning themselves from nicotine delivered via the devices, and a large online survey of e-cigarette users demonstrated that these devices ended up being used for longer durations than typical nicotine replacement therapies [41–43]. Not surprisingly, this combination of factors has led to the most common pattern of usage being dual use of e-cigarettes and conventional cigarettes [44]. Given the growing and widespread use of e-cigarettes as both a treatment for TUD and for recreational use, further studies are needed for an improved understanding of the impact of these devices on health and smoking behavior.

Review Questions

1. CK is a 67-year-old Asian American female with history of schizophrenia, hyperlipidemia, and hypertension who presents to your primary care clinic for her yearly check-up. She is insured through a private healthcare insurance company. Which of DL's demographic characteristics have been associated with a higher prevalence of smoking?
   A. Gender
   B. Age
   C. Mental health diagnosis
   D. Ethnicity
   E. Insurance coverage

   Answer: C

   Explanation: Individuals with mental health diagnoses have higher rates of smoking compared to the general population. Males, aged 24–65, American Indian, Alaska native, or multiracial, uninsured or insured by Medicaid have a higher prevalence of smoking (none of which categories CK falls into—female, age >65, Caucasian, has private insurance).
2. AH is a 52-year-old male with no prior medical history who is interested in non-pharmacological therapy for his tobacco use disorder. He has never received any nonpharmacological therapy for his TUD and has never received psychotherapy. Which of the following nonpharmacological therapies is most commonly and widely used, and would be most appropriate for treatment of AH's tobacco use disorder?
   F. Acceptance and commitment therapy (ACT)
   G. Cognitive behavioral therapy (CBT)
   H. Dialectical behavioral therapy (DBT)
   I. Exposure therapy
   J. Mindfulness-based therapy

   Answer: B

   Explanation: Cognitive behavioral therapy (CBT) is the most commonly and widely used nonpharmacological therapy for Tobacco Use Disorder. Since AH has never received any nonpharmacological therapy or psychotherapy and has no comorbidities, CBT would be the most appropriate as a first-line therapy.
3. LK is a 37-year-old male with history of epilepsy, bipolar disorder type II, and tobacco use disorder who was discharged 1 week ago after being hospitalized for suicidal ideation. He smokes 2 packs of cigarettes per day and smokes his first cigarette within 5 minutes after waking up and has never tried any pharmaco-therapy for TUD. Which would be most appropriate pharmacological treatment option for LK?
   A. Nicotine patch monotherapy
   B. Nicotine patch with nicotine gum

C. Bupropion
D. Varenicline
E. Clonidine

Answer: B

Explanation: Combination nicotine replacement therapy is the most appropriate choice since it is a first-line pharmacological therapy and safest option in this patient. Since this patient was recently hospitalized for suicidal ideation, varenicline would not be appropriate since it has only been shown to be safe in patients who have had stable psychiatric symptoms for 6 months. Bupropion is contraindicated given his history of epilepsy. Nicotine patch monotherapy and clonidine are not as effective as combination NRT.

4. TL is a 28-year-old female with tobacco use disorder. She smokes 1.5 packs of cigarettes per day and smokes her first cigarette 45 minutes after waking up. Which strength of nicotine patch and nicotine lozenge would be most appropriate to initiate in TL based on her level of tobacco dependence?
   A. 21 mg nicotine patch with 4 mg nicotine lozenge
   B. 21 mg nicotine patch with 2 mg nicotine lozenge
   C. 14 mg nicotine patch with 4 mg nicotine lozenge
   D. 14 mg nicotine patch with 2 mg nicotine lozenge
   E. 7 mg nicotine patch with 2 mg nicotine lozenge

   Answer: B

   Explanation: Using the HIS, TL has 3 points (1 point for smoking 30–60 min after waking and 2 points for smoking 30 cigarettes/day) and moderate tobacco dependence. Therefore, she should be initiated on the 21 mg nicotine patch with the 2 mg nicotine lozenge.
5. SH is a 30-year-old female who is interested in using electronic cigarettes to quit smoking and presents to your clinic to learn more about them. Which of the following statements would be the most accurate for you to tell SH regarding electronic cigarettes?
   A. Electronic cigarettes appear to deliver fewer harmful chemicals to the body than conventional cigarettes.
   B. Electronic cigarettes are regulated by the FDA.
   C. Electronic cigarettes are FDA-approved for treatment of tobacco use disorder.
   D. Electronic cigarette use does not carry a risk for nicotine dependence.
   E. Only previous/current smokers use electronic cigarettes.

   Answer: A

   Explanation: Electronic cigarettes appear to deliver fewer harmful chemicals to the body than conventional cigarettes. They are not regulated by the FDA, are not FDA-approved for treatment of tobacco use disorder, and carry a risk for nicotine dependence. Electronic cigarettes are increasingly used among youth/adolescents and may serve as a gateway to conventional cigarettes.

References

1. Wang TW, Asman K, Gentzke AS, Cullen KA, Holder-Hayes E, Reyes-Guzman C, et al. Tobacco product use among adults - United States, 2017. MMWR Morb Mortal Wkly Rep. 2018;67:1225–32.
2. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. JAMA. 2000;284:2606–10.
3. United States Surgeon General. The health consequences of smoking – 50 Years of progress: a report of the surgeon general: (510072014-001) [Internet]. American Psychological Association; 2014 [cited 2019 Jan 4]. Available from: http://doi.apa.org/get-pe-doi.cfm?doi=10.1037/e510072014-001.
4. Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, et al. 21st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med. 2013;368:341–50.
5. Xu X, Bishop EE, Kennedy SM, Simpson SA, Pechacek TF. Annual healthcare spending attributable to cigarette smoking: an update. Am J Prev Med. 2015;48:326–33.
6. Benowitz NL, Hukkanen J, Jacob P. Nicotine chemistry, metabolism, kinetics and biomarkers. Handb Exp Pharmacol. 2009:29–60.
7. Benowitz NL. Clinical pharmacology of nicotine: implications for understanding, preventing, and treating tobacco addiction. Clin Pharmacol Ther. 2008;83:531–41.
8. Cameron JM, Howell DN, White JR, Andrenyak DM, Layton ME, Roll JM. Variable and potentially fatal amounts of nicotine in e-cigarette nicotine solutions. Tob Control. 2014;23:77–8.
9. Solarino B, Rosenbaum F, Rießelmann B, Buschmann CT, Tsokos M. Death due to ingestion of nicotine-containing solution: case report and review of the literature. Forensic Sci Int. 2010;195:e19–22.
10. Nicotine Poisoning | California Poison Control System | UCSF [Internet]. [cited 2019 Jan 4]. Available from: https://calpoison.org/news/nicotine-poisoning.
11. Substance-Related and Addictive Disorders. Diagn Stat Man Ment Disord [Internet]. American Psychiatric Association; 2013 [cited 2019 Jan 4]. Available from: https://doi.org/10.1176/appi.books.9780890425596.dsm16.
12. Panel TU and DG. Treating tobacco use and dependence: 2008 update. US Department of Health and Human Services; 2008.
13. Siu AL, Preventive Services Task Force US. Behavioral and pharmacotherapy interventions for tobacco smoking cessation in adults, including pregnant women: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2015;163:622–34.
14. John U, Meyer C, Schumann A, Hapke U, Rumpf H-J, Adam C, et al. A short form of the Fagerström Test for Nicotine Dependence and the Heaviness of Smoking Index in two adult population samples. Addict Behav. 2004;29:1207–12.
15. O'Connor RJ. Non-cigarette tobacco products: what have we learned and where are we headed? Tob Control. 2012;21:181–90.
16. Ebbert JO, Elrashidi MY, Stead LF. Interventions for smokeless tobacco use cessation. Cochrane Database Syst Rev. 2015:CD004306.
17. Lancaster T, Stead LF. Individual behavioural counselling for smoking cessation. Cochrane Database Syst Rev. 2017;3:CD001292.
18. Stead LF, Carroll AJ, Lancaster T. Group behaviour therapy programmes for smoking cessation. Cochrane Database Syst Rev. 2017;3:CD001007.
19. Perkins KA, Karelitz JL, Jao NC. Optimal carbon monoxide criteria to confirm 24-hr smoking abstinence. Nicotine Tob Res. 2013;15:978–82.
20. Clinical Practice A. Guideline for treating tobacco use and dependence: 2008 update. Am J Prev Med. 2008;35:158–76.
21. Kerr S, Woods C, Knussen C, Watson H, Hunter R. Breaking the habit: a qualitative exploration of barriers and facilitators to smoking cessation in people with enduring mental health problems. BMC Public Health. 2013;13:221.

22. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev [Internet]. 2013 [cited 2019 Mar 1]; Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009329.pub2/abstract.
23. Hsia SL, Myers MG, Chen TC. Combination nicotine replacement therapy: strategies for initiation and tapering. Prev Med. 2017;97:45–9.
24. DailyMed – NICODERM CQ- nicotine patch, extended release [Internet]. [cited 2019 Jan 6]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=93b2d1b9-83c1-40b5-b6af-90c38c8d6cef.
25. DailyMed – NICOTINE GUM- nicotine polacrilex gum, chewing [Internet]. [cited 2019 Jan 6]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3872c622-1a30-459c-b878-61648bb30627.
26. ZYBAN (bupropion hydrochloride) Sustained-Release Tablets [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2017.
27. Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. Lancet. 2016;387:2507–20.
28. CHANTIX (varenicline tartrate) [package insert]. New York, NY: Pfizer Labs; 2019. Available from: http://labeling.pfizer.com/showlabeling.aspx?id=557.
29. Health CO on S and. Smoking and Tobacco Use; Electronic Cigarettes [Internet]. Cent Dis Control Prev. 2018 [cited 2019 Jan 17]. Available from: https://www.cdc.gov/tobacco/basic_information/e-cigarettes/index.htm.
30. Hutzler C, Paschke M, Kruschinski S, Henkler F, Hahn J, Luch A. Chemical hazards present in liquids and vapors of electronic cigarettes. Arch Toxicol. 2014;88:1295–308.
31. Marsot A, Simon N. Nicotine and cotinine levels with electronic cigarette: a review. Int J Toxicol. 2016;35:179–85.
32. Cantrell J, Huang J, Greenberg M, Willett J, Hair E, Vallone D. History and current trends in the electronic nicotine delivery systems retail marketplace in the United States: 2010–2016. Nicotine Tob Res. 2018;1–5. https://doi.org/10.1093/ntr/nty214.
33. Grana RA, Ling PM, Benowitz N, Glantz S. Electronic cigarettes. Cardiology patient page. Circulation. 2014;129:e490–2.
34. McMillen RC, Gottlieb MA, Shaefer RMW, Winickoff JP, Klein JD. Trends in electronic cigarette use among U.S. adults: use is increasing in both smokers and nonsmokers. Nicotine Tob Res. 2015;17:1195–202.
35. Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tob Control. 2014;23:133–9.
36. Ruprecht AA, De Marco C, Pozzi P, Munarini E, Mazza R, Angellotti G, et al. Comparison between particulate matter and ultrafine particle emission by electronic and normal cigarettes in real-life conditions. Tumori. 2014;100:e24–7.
37. Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead L, Hajek P. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev [Internet]. 2016; Available from: https://doi.org/10.1002/14651858.CD010216.pub3.
38. Liu X, Lu W, Liao S, Deng Z, Zhang Z, Liu Y, et al. Efficiency and adverse events of electronic cigarettes: a systematic review and meta-analysis (PRISMA-compliant article). Medicine (Baltimore). 2018;97:e0324.
39. Barrington-Trimis JL, Urman R, Berhane K, Unger JB, Cruz TB, Pentz MA, et al. E-cigarettes and future cigarette use. Pediatrics. 2016;138
40. Dutra LM, Glantz SA. Electronic cigarettes and conventional cigarette use among U.S. adolescents: a cross-sectional study. JAMA Pediatr. 2014;168:610–7.
41. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of "vapers" who had achieved complete substitution of smoking. Subst Abuse. 2013;7:139–46.

42. Dawkins L, Turner J, Roberts A, Soar K. “Vaping” profiles and preferences: an online survey of electronic cigarette users. Addiction. 2013;108:1115–25.
43. Etter J-F, Bullen C. A longitudinal study of electronic cigarette users. Addict Behav. 2014;39:491–4.
44. QuickStats: Cigarette smoking status among current adult E-cigarette users, by age group — National Health Interview Survey, United States, 2015. MMWR Morb Mortal Wkly Rep [Internet]. 2016 [cited 2019 Jan 17];65. Available from: https://www.cdc.gov/mmwr/volumes/65/wr/mm6542a7.htm.

Alcohol

8

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High-Yield Review Points

- Risk factors for alcohol use disorder include family history of alcoholism, male sex, and early onset of alcohol use.
- Individuals with specific polymorphisms in the genes coding for alcohol dehydrogenase and aldehyde dehydrogenase, the two main enzymes involved in alcohol metabolism, are at decreased risk of alcohol use disorder.
- Alcohol withdrawal can lead to a range of symptoms including seizures and delirium. The most commonly used instrument to assess withdrawal symptoms is the Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar).
- There are three FDA-approved pharmacotherapies for alcohol use disorder: naltrexone, a mu-opioid receptor antagonist; acamprosate, a modulator of glutamatergic neurotransmission; and disulfiram, a medication that causes adverse reactions to alcohol by inhibiting aldehyde dehydrogenase.
- Laboratory markers are used to monitor alcohol consumption. Direct markers are products of alcohol metabolism and include ethyl glucuronide, ethyl sulfate, and phosphatidylethanol. Indirect markers reflect alcohol's effects on organ systems and cellular function and include GGT, AST, ALT, CDT, and MCV.

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Epidemiology

Alcohol use remains one of the most important risk factors for death and disability worldwide [1] and was directly responsible for 34,865 deaths in the United States in 2016 [2]. Alcohol-related mortality has been gradually increasing over the past decade [3]. Findings from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) indicate that the 12-month prevalence of alcohol use disorder (AUD) is 13.9%, with higher rates in males than females (17.6% vs. 10.4%) [4]. This survey also found that the prevalence of alcohol use, risky drinking, and alcohol use disorders is increasing [5], which is in line with the higher rates of alcohol-related mortality observed nationally.

There are important sex differences in both the prevalence and progression of alcohol use disorder. An earlier iteration of NESARC found that alcohol use disorder was 2.5 times more prevalent in men compared to women [6]. These sex differences appear to be diminishing over time as the most recent NESARC findings indicate that the male to female ratio for alcohol use disorder is 1.7:1 [4]. Additional findings from the Centers for Disease Control and Prevention (CDC) suggest that 10% of pregnant women consumed alcohol in the past 30 days [7] and there is concern that the rising prevalence of alcohol use disorder among women could lead to higher levels of alcohol use in pregnancy. Women also tend to experience a more rapid progression from first alcohol exposure to development of an alcohol use disorder when compared to men, a phenomenon known as telescoping [8]. Women who develop problematic alcohol-related behaviors should therefore be closely monitored for progression and offered appropriate counseling.

Binge drinking, defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as consuming five or more drinks for men or four or more drinks for women in a single occasion, peaks in young adulthood and then gradually declines with age [9]. This concords with the 12-month prevalence of AUD, which also peaks during young adulthood and declines with age [4]. Age of onset of alcohol use is thought to be an important risk factor for AUD; individuals who start drinking at a younger age are at greater risk [10]. Two "typologies" of AUD have been formulated by Cloninger based in part on age of onset of heavy alcohol use: Type I Alcoholism develops after age 25, affects both men and women equally, and tends to respond better to treatment whereas Type II Alcoholism develops before age 25, affects males more than females (especially "sons of male alcoholics"), and tends to be associated with antisocial behavior [11]. However, these typologies are likely an oversimplification of the wide range of phenotypic variability that is observed in alcohol use disorder.

The Genetics of Alcohol Use Disorder

Family history of alcoholism is an established risk factor for alcohol use disorder and is listed under the genetic and physiological risk factors in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [12]. Individuals

with a family history of alcoholism may have an inherent preference for ethanol. For example, there is evidence that healthy social drinkers with a family history of alcoholism consume substantially more alcohol in laboratory settings [13]. Aggregated data from twin studies suggest that alcoholism is approximately 50% heritable [14]. Despite this, only a small proportion of the genes that are associated with alcohol use disorder have been identified thus far.

Polymorphisms in genes involved in alcohol metabolism have been most consistently linked with alcohol use disorder. Ethanol is metabolized in a two-step process: alcohol dehydrogenase converts ethanol to acetaldehyde and then aldehyde dehydrogenase metabolizes acetaldehyde to acetate. A variant of the alcohol dehydrogenase 1B gene leads to rapid alcohol metabolism and decreases the risk of alcohol use disorder in individuals of European and Asian ancestry [15–17], whereas a different polymorphism in the same gene has a similar effect in individuals of African ancestry [16]. Alterations in the second step of alcohol metabolism can also affect AUD risk. In individuals of Asian ancestry, a less functional variant of aldehyde dehydrogenase 2 protects against alcoholism by causing a buildup of acetaldehyde during drinking which may induce flushing, nausea, and tachycardia [15, 18]. Individuals who are heterozygous for this allele but continue to consume alcohol are at increased risk of esophageal cancer, as acetaldehyde is also a known carcinogen [19]. Patients with a history of alcohol-induced flushing should therefore be counseled to limit their alcohol intake.

Pharmacokinetics

Alcohol is absorbed primarily by passive diffusion in the duodenum and the jejunum and to a lesser degree in the stomach [20]. As a result, the rate of gastric emptying plays an important role in the rate of absorption. The presence of food in the stomach slows down the rate of gastric emptying, which greatly reduces absorption [20]. When advising patients about alcohol use, it is always helpful to caution against drinking on an empty stomach.

Alcohol is primarily eliminated in the liver and to a lesser degree in the GI tract. In the first step of metabolism, alcohol is metabolized to acetaldehyde by alcohol dehydrogenase, and then, in the second step, acetaldehyde is oxidized to acetate by the enzyme aldehyde dehydrogenase. Alcohol is also metabolized to a lesser extent by a cytochrome P450-dependent ethanol-oxidizing system.

In general, after consuming a single standard drink, the amount of alcohol in a drinker's blood peaks within 30–45 minutes (a "standard drink" is defined by NIAAA as containing 14 grams of pure ethanol, typically about 1.5 ounces of distilled spirits, 5 ounces of wine, or 12 ounces of beer) [21]. However, absorption and metabolism vary according to a person's age, height, sex, weight, liver function, and recent food consumption. In addition to metabolism in the liver, alcohol is oxidized by certain isoforms of alcohol dehydrogenase in the stomach. Certain medications inhibit gastric alcohol dehydrogenase activity, such as the H2 blockers cimetidine and ranitidine [22]. The activity of gastric alcohol

dehydrogenase is also reported to be lower in women [21], which may explain in part why women have greater blood alcohol levels compared to men following a fixed dose of alcohol. Females also tend to have a greater percentage of body fat and less total body water than males, which is another important reason for this phenomenon [21].

Pharmacodynamics

Alcohol has pharmacodynamic effects on a wide range of neurotransmitter systems. For the sake of simplicity, this chapter will focus on two systems: the GABAergic system and the glutamatergic system.

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain and consists of two main receptor subtypes: $GABA_A$ and $GABA_B$. $GABA_A$ receptors are ligand-gated ion channels that, when activated, allow the inflow of negative chloride ions (Cl^-) which hyperpolarize the neuron, whereas $GABA_B$ is a metabotropic G-coupled receptor. Acute alcohol intake increases $GABA_A$ activity through direct effects on the receptor and indirect effects such as increased presynaptic GABA release [23]. Chronic alcohol intake leads to several neuroadaptations within the GABAergic system that are thought to play a role in the development of physiologic dependence.

Glutamate is the most abundant excitatory neurotransmitter in the human brain. Glutamate receptors include three major classes of ionotropic receptors: α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors, *N*-methyl-D-aspartate (NMDA) receptors, and kainate receptors. NMDA receptors are typically inhibited by acute ingestion of ethanol [24]. Conversely, chronic ethanol exposure upregulates NMDA receptors, enhances their functionality, and increases NMDA receptor-mediated glutamatergic synaptic transmission [25]. It is thought that alcohol withdrawal-related hyperexcitability is due to increases in NMDA receptor transmission; this may also explain the enhanced susceptibility to seizures during withdrawal [25]. The mechanisms by which chronic ethanol consumption enhances NMDA receptor function are still not fully understood and continue to be an area of active research.

Alcohol Intoxication

Alcohol intoxication occurs when alcohol accumulates in the blood stream, with signs and symptoms varying depending upon the type and amount of alcohol consumed, rate of intake, and the frequency and pattern of use. In individuals who do not abuse alcohol, the clinical effects of alcohol intoxication are relatively predictable with neurologic, gastrointestinal, and cardiovascular effects that are usually related to blood alcohol concentration (BAC). Conversely, after a long

history of chronic alcohol abuse, individuals can develop tolerance. When tolerance develops, the effects of alcohol can become unpredictable with some showing little or no signs of intoxication even with high BACs.

Among individuals who do not consume alcohol heavily and chronically, associated symptoms with each BAC range are as follows [26, 27]:

- BAC between 10 mg/dl and 100 mg/dl: relaxation, mild impairment of attention or memory, increased talkativeness, mild deficits in coordination.
- BAC between 100 mg/dl and 200 mg/dl: ataxia, greater deficits in attention, slurred speech, prolonged reaction time, nystagmus, impaired judgment, behavioral changes.
- BAC between 200 mg/dl and 300 mg/dl: lack of coordination, severely impaired attention, amnesia, dysarthria, hypothermia, nausea, vomiting.
- BAC exceeding 300 mg/dl: stupor, loss of consciousness, coma, respiratory depression, death.

Management of Alcohol Intoxication

The treatment for isolated, acute alcohol intoxication is primarily supportive. Clinical management typically occurs in the emergency department. Initial evaluation should include an airway assessment, observation of respiratory function, and measurement of vital signs. The patient should be placed in a lateral position to prevent aspiration [28]. Individuals should also be carefully assessed for traumatic injuries and should be asked whether they have ingested or otherwise taken other drugs or potentially harmful substances. Obtaining history from the patient can be difficult, so additional information may need to be collected from paramedics, witnesses at the scene, friends, and family members [29]. A toxicology screen can be helpful to determine whether other substances were co-ingested [29]. If co-ingestion of methanol, ethylene glycol, or other substances is suspected, treatment should be modified to address these substances.

Patients with moderate to severe ethanol intoxication may present with volume depletion, malnutrition, and electrolyte abnormalities. Since altered mental status can be caused by hypoglycemia, a finger-stick glucose test should be performed [30]. Intravenous fluids should be administered to correct fluid and electrolyte abnormalities, but in those with suspected thiamine deficiency, intravenous thiamine should be given prior to glucose administration to prevent the precipitation of Wernicke's encephalopathy [28]. If the patient is experiencing nausea or vomiting, the use of antiemetic drugs may be indicated [28]. Individuals should be closely monitored with serial examinations until clinical sobriety has been achieved. Any acute changes in clinical status or alteration in the level of consciousness should be immediately investigated.

Alcohol Withdrawal

Alcohol withdrawal is a potentially life-threatening condition. Symptoms of alcohol withdrawal usually begin 6 to 24 hours after the cessation of drinking and may develop while patients still have an elevated blood alcohol concentration [31]. Withdrawal symptoms are thought to be due to central nervous system hyperactivity and may include anxiety, irritability, agitation, tremor, headache, diaphoresis, insomnia, nausea, and vomiting [31, 32]. Elevated blood pressure and tachycardia can occur. Severe withdrawal syndromes include alcohol withdrawal seizures, alcoholic hallucinosis, and delirium tremens (DTs), which are discussed individually below.

Withdrawal seizures are typically generalized tonic-clonic seizures that occur within 6–48 hours after the last alcoholic drink [33]. While status epilepticus is rare, multiple seizures can occur [33]. Untreated withdrawal seizures may progress to delirium tremens in nearly one-third of patients [34]. Therefore, irrespective of the measured withdrawal severity scores, the occurrence of seizures during the alcohol withdrawal period is indicative of severe alcohol withdrawal and merits aggressive treatment.

Alcoholic hallucinosis refers to hallucinations that typically develop within 12–24 hours of abstinence [32]. Hallucinations can be visual, auditory, or tactile in nature. The presence of hallucinations with normal vital signs and a clear sensorium is a hallmark of this disorder [34]. Because individuals know they are hallucinating, this condition can be quite distressing. Most cases typically resolve within 48 hours [32]. Alcoholic hallucinosis is not synonymous with delirium tremens. Though hallucinations may be present in both, alcoholic hallucinosis presents with a clear sensorium and normal vital signs.

The most severe form of alcohol withdrawal is delirium tremens, in which drinkers who have recently abstained from alcohol or reduced their alcohol intake develop symptoms of withdrawal and delirium (an acute-onset disturbance in attention, awareness, and cognition that fluctuates in intensity during the day) [35]. Delirium tremens may present with tachycardia, hypertension, hyperthermia, and diaphoresis [36]. This syndrome typically begins 48–72 hours after the last drink and may last over a week, although most cases resolve within 2–3 days [36]. There are a number of risk factors for developing delirium tremens, including a previous history of delirium tremens, history of withdrawal seizures, older age, comorbid medical illnesses, and Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) scores greater than 15 [35]. Delirium tremens is a life-threatening condition, the present-day mortality ranges between 1 and 4% in hospitalized patients [35]. Death most commonly occurs due to arrhythmias, hyperthermia, or complications due to comorbid conditions [35].

Management of Alcohol Withdrawal

The primary goals of managing alcohol withdrawal are alleviation of symptoms, prevention of progression, and identification and correction of metabolic derangements. Correction of fluid and electrolyte abnormalities should be performed

using intravenous fluids and nutritional supplementation. In those with an extensive drinking history, thiamine should be administered prior to glucose to prevent precipitation of Wernicke's encephalopathy. Vital signs should be closely monitored.

Medication management is needed in individuals with a history of severe withdrawal (e.g., seizures or delirium tremens) and those who demonstrate moderate to severe symptoms of withdrawal at presentation or go on to develop such symptoms [31]. Benzodiazepines are recommended to treat symptoms of alcohol withdrawal and can be given using a fixed-schedule or symptom-triggered approach [32]. In the symptom-triggered approach, the Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar), a 10-item scale with scores ranging from 0 to 67, is typically utilized to assess the severity of alcohol withdrawal symptoms [32]. Benzodiazepines are then given to the patient when severity scores exceed a certain threshold. As an example of a symptom-triggered treatment regimen, the CIWA-Ar could be administered every hour and then 2-4 mg of lorazepam could be given when the CIWA-Ar score is greater or equal to 8 [32]. Although symptom-triggered regimens lead to the administration of less medication and shorten the duration of treatment [32], they require monitoring by a healthcare professional and are not recommended for outpatient detoxification [31]. In a fixed-schedule dosing regimen, benzodiazepines are given at fixed intervals even in the absence of active symptoms of withdrawal. Fixed-schedule dosing should be used in individuals with a history of withdrawal seizures regardless of CIWA-Ar score [31]. Long-acting benzodiazepines such as diazepam and chlordiazepoxide are commonly used with both approaches, but treatment with lorazepam and oxazepam is preferable in the elderly and patients with liver disease [32].

Management of withdrawal seizures Alcohol withdrawal seizures are a medical emergency. A thorough evaluation is necessary to rule out other causes of seizures, including electrolyte disturbances and traumatic brain injury. Individuals with withdrawal seizures should be treated with an intravenous benzodiazepine [31]. The patient should then be monitored and appropriately treated for other symptoms of withdrawal [31]. The majority of withdrawal seizures do not require treatment with non-benzodiazepine anticonvulsant medications.

Management of delirium tremens Individuals with delirium tremens should be closely observed and their vital signs should be frequently monitored. This should ideally be done in a quiet room with good lighting and environmental cues such as a calendar and clock. Those with severe delirium tremens may need to be placed in an intensive care unit for continuous monitoring [31]. Physical restraints may be temporarily required in cases of severe agitation for the protection of both the patient and staff [36]. A thorough evaluation should be performed to rule out concurrent medical conditions and other causes of delirium. Fluid and electrolyte abnormalities, hyperthermia, and high blood pressure should be appropriately managed [31] and intravenous thiamine should be administered [35]. Sedative-hypnotic medications are recommended as the mainstay treatment; intravenous benzodiazepines are most commonly used [36].

The goal of treatment is to give sufficient medication in order to achieve and maintain light somnolence, a state in which the patient falls asleep unless stimulated but is easily aroused [36].

Laboratory Screening for Alcohol Use

Direct biomarkers are products of ethanol metabolism and include ethyl glucuronide (EtG), ethyl sulfate (EtS), and phosphatidylethanol (PEth).

- *Ethyl glucuronide (EtG)* is a metabolite of alcohol that is formed by enzymatic conjugation of ethanol with glucuronic acid. It can be collected from a variety of bodily fluids and tissues but is most commonly measured in the urine. Although urine EtG can remain positive for up to 5 days following heavy alcohol consumption [37], its sensitivity is highest within the first 24 hours after drinking [38, 39].
- *Ethyl sulfate (EtS)* is an alcohol metabolite formed by enzymatic conjugation of activated sulfate and ethanol. The time course for its detection in the urine following ethanol consumption is similar to EtG [37].
- *Phosphatidylethanol (PEth)* refers to a group of ethanol metabolites formed through a phospholipase D-mediated reaction of ethanol with phosphatidylcholine. PEth is measured in whole blood and can remain detectable in blood for up to 2 weeks after abstinence [40].

Indirect biomarkers reflect the toxic effects of ethanol on organs, tissues, or body biochemistry. These include gamma-glutamyltransferase (GGT), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), carbohydrate-deficient transferrin (CDT), and mean corpuscular volume (MCV).

- *Gamma-glutamyltransferase (GGT)* is an enzyme which can be elevated after several weeks of heavy drinking [41]**.** Elevated GGT is not specific for alcohol use, levels can be elevated in other conditions such as viral hepatitis and liver injury due to hepatotoxins [31]. Levels typically return to normal after 2–6 weeks of abstinence [41].
- *Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)* are enzymes that are elevated secondary to hepatic injury. An AST/ALT ratio of greater than 2 may be indicative of alcohol-related liver disease [41].
- *Carbohydrate-deficient transferrin (CDT)* refers to isoforms of transferrin that are deficient of sialic acid due to alcohol use. CDT levels are elevated following consumption of 60–80 grams of alcohol per day for 2–3 weeks and return to normal after 2–4 weeks of abstinence [41]. Although false positives can occur, CDT is far more specific than GGT for detecting alcohol use [41].
- *Mean corpuscular volume (MCV)* is a measure of red blood cell size and can be altered due to the direct effect of alcohol on erythroblast development [41]. It has low sensitivity and can take several months to return to normal following abstinence [41], so it has limited utility as an indicator of relapse.

Diagnosing Alcohol Use Disorder

Screening There are a range of screening tools for alcohol use disorder, but this chapter will focus on two: The Alcohol Use Disorders Identification Test (AUDIT) and the CAGE questionnaire. The AUDIT is a 10-item screening tool developed by the World Health Organization. It has three domains which assess consumption ("hazardous alcohol use"), dependence symptoms, and consequences of drinking ("harmful alcohol use") [42]. Responses to each of the ten items are scored from 0–4 with total scores ranging from 0–40; scores of 8 points or more are usually used as an indicator of problematic drinking [42]. The CAGE questionnaire is a four-item acronym questionnaire. Scores of 2 or more are considered a positive screening [43] and indicate that the patient warrants further assessment for alcohol use disorder.

Diagnosis The DSM-5 defines alcohol use disorder as "a problematic pattern of alcohol use leading to clinically significant impairment or distress" [12]. The manual requires that individuals meet at least 2 of 11 diagnostic criteria over a 12-month period to be diagnosed with the disorder. The severity of diagnosis is based on symptom counts. Individuals with 2–3 symptoms have mild AUD, those with 4–5 symptoms have moderate AUD, and individuals with 6 or more symptoms have severe AUD [12]. Alcohol use disorder is defined as being in early remission if no criteria (except craving) have been met for at least 3 months but less than 12 months and in sustained remission if no criteria have been met (except craving) for 12 months or longer [12].

Pharmacotherapy for Alcohol Use Disorder

Both psychotherapy and pharmacotherapy are effective treatments for alcohol use disorder [44]. In clinical practice, these two modalities are often used in tandem. Psychotherapies for substance use disorders are described elsewhere in this volume, therefore the remainder of this chapter will focus exclusively on pharmacotherapy.

FDA-Approved Pharmacotherapies There are currently three pharmacotherapies approved by the Food and Drug Administration (FDA) for alcohol use disorder: disulfiram, naltrexone, and acamprosate (for dosages and common side effects, see Table 8.1).

- *Disulfiram* was the first available FDA-approved pharmacotherapy for the treatment of alcohol use disorder. It inhibits the enzyme aldehyde dehydrogenase, leading to a buildup of acetaldehyde that can cause nausea, vomiting, flushing, sweating, tachycardia, palpitations, hypotension, hyperventilation, and rarely serious cardiovascular issues [45, 46]. Disulfiram functions as a form of aversion therapy; patients avoid drinking due to fear of a disulfiram-ethanol reaction. Although findings related to the effectiveness of disulfiram are mixed, there is evidence that the medication may be more effective when adherence is supervised

Table 8.1 FDA-approved pharmacotherapies for alcohol use disorder [46]

	Disulfiram	Naltrexone	Acamprosate
Dose	250–500 mg PO daily	50 mg PO daily (oral) 380 mg IM q28 days (IM)	666 mg PO TID
Absolute contraindications	Use of metronidazole, paraldehyde, or alcohol-containing products Hypersensitivity to disulfiram Severe cardiac disease Psychosis	Acute hepatitis/liver failure Active opioid use, failed naloxone challenge, positive urine drug screen for opioids, or acute opioid withdrawal Hypersensitivity to naltrexone	Severe renal impairment (CrCl <30 ml/min) Hypersensitivity to acamprosate
Relative contraindications	Hepatic disease Diabetes Pregnancy (category C)	Active liver disease Serum aminotransferases 5 times upper levels Pregnancy (category C) Bleeding or coagulation disorder (IM formulation)	Pregnancy (category C)
Common side effects	Drowsiness Fatigue Acne Allergic dermatitis Headache Impotence Metallic or garlic aftertaste	Nausea Vomiting Dizziness Headache Somnolence Fatigue Injection site reactions (IM formulation)	Diarrhea Flatulence Nausea Vomiting Anxiety Pruritis Somnolence
Severe side effects	Hepatotoxicity Optic neuritis Peripheral neuropathy Psychosis	Precipitated withdrawal Hepatotoxicity Depression and suicidality	Suicidality
Baseline laboratory tests	Liver function tests Pregnancy test Breathalyzer (if clinically indicated)	Urine toxicology screen Liver function tests Pregnancy test	Renal function tests Pregnancy test
Clinical notes	Patients must abstain from alcohol for >12 hours prior to initiation. Avoid products containing alcohol, reactions can occur up to 14 days after last use of disulfiram. Monitor liver function tests	Blocks effects of opioid analgesics. Patients should be opioid free for a minimum of 7–10 days. Provide patients with documentation stating that they are taking naltrexone. Monitor liver function tests	Can be used in patients with hepatic impairment. Modify dose in patients with moderate renal impairment (CrCl 30–50 ml/min)

[47]. Due to the potential for adverse effects, disulfiram should only be used in patients that are currently abstinent and is not intended for use in active drinkers. Patients should wait at least 12 hours since their last drink before starting disulfiram [46]. As disulfiram binds irreversibly to aldehyde dehydrogenase, it can take up to 2 weeks after discontinuation before the patient can drink without

inducing a disulfiram-ethanol reaction [46]. Due to the potential for hepatotoxicity, it is recommended to obtain baseline liver function tests prior to initiating treatment and repeat testing 2 weeks after starting the medication [46]. Liver function tests should then be monitored monthly for the first 6 months of treatment and every 3 months thereafter [46].

- *Naltrexone* is a nonselective opioid receptor antagonist that has been shown to reduce relapse to drinking and return to binge drinking when compared to placebo [48]. It is available in both oral and long-acting injectable formulations. Given that naltrexone blocks mu-opioid receptors, individuals who are prescribed naltrexone should be screened for recent opioid use and naltrexone should not be administered if opioids have been used within the past 7–10 days due to the risk of precipitated withdrawal. Naltrexone should also be avoided if opioid administration is anticipated in the near future (e.g., an upcoming surgery requires opioid analgesia). The FDA has issued a black-box warning for hepatotoxicity, although this tends to be associated with higher doses of naltrexone than the typical dose used clinically [46]. Nonetheless, liver function tests should be measured at baseline and monitored periodically [46].
- *Acamprosate* is a medication that is thought to modulate glutamatergic neurotransmission [49]. It is typically initiated after at least 5 days of abstinence but can be used safely in patients actively consuming alcohol [46]. This medication is typically well tolerated; diarrhea is the most common side effect. Prior to initiation of acamprosate, it is important to obtain baseline renal function tests as it is excreted exclusively by the kidneys. Due to the lack of hepatic metabolism, it can be used safely in individuals with hepatic impairment or severe liver disease [46].

Non-FDA-Approved Pharmacotherapies There are multiple medications that are used as off-label treatments for alcohol use disorder. We will discuss three of the most commonly used medications: topiramate, gabapentin, and baclofen (for dosages and common side effects, see Table 8.2). Additionally, the opioid antagonist nalmefene is approved for the treatment of alcohol use disorder in Europe but is not discussed here.

- Topiramate is an FDA-approved treatment for epilepsy and migraine. There is meta-analytic evidence from randomized controlled trials that treatment with topiramate is associated with decreased drinking days, drinks per drinking day, and heavy drinking days when compared with placebo [48]. Topiramate decreases excitatory neurotransmission by acting on AMPA and kainate receptors and increases inhibitory neurotransmission by enhancing GABA-A conduction [50]. Topiramate also inhibits carbonic anhydrase and acts on several other types of receptors, including L-type calcium channels and voltage-dependent sodium channels [50].
- Gabapentin targets voltage-gated calcium channels and is FDA-approved as a treatment for postherpetic neuralgia and as an adjunctive therapy for epilepsy. Several small trials have found that gabapentin is effective at reducing alcohol

Table 8.2 Off-label medications for alcohol use disorder

	Topiramate	Gabapentin	Baclofen
Dose	25 mg PO daily – 150 mg PO BID	300 mg PO BID – 600 mg PO TID	5 – 20 mg PO TID Maximum: 20 mg PO QID
Absolute contraindications	None	Hypersensitivity to gabapentin	Hypersensitivity to baclofen
Relative contraindications	Pregnancy (category D, increased risk of cleft lip and/or palate)	Severe renal impairment (CrCl <30 ml/minute) Pregnancy (category C)	Severe renal impairment Pregnancy (category C)
Common side effects	Cognitive dysfunction Paresthesias Taste abnormalities Anorexia Weight loss Nervousness Fatigue Somnolence Dizziness	Dizziness Somnolence Fatigue Ataxia Nystagmus Peripheral edema	Drowsiness Dizziness Weakness Confusion Headache Nausea Insomnia
Severe side effects	Nephrolithiasis Hyperammonemia Suicidality Metabolic acidosis Hyperthermia Acute myopia/glaucoma	Anaphylaxis and angioedema Suicidality Drug reaction with eosinophilia and systemic symptoms (DRESS)	Severe withdrawal (symptoms can include seizures, hallucinations, hyperpyrexia and death)
Baseline laboratory tests	Renal function tests Serum bicarbonate Pregnancy test	Renal function tests Pregnancy test	Renal function tests Pregnancy test
Clinical notes	Primarily excreted unchanged in the urine. Dose should be modified in patients with renal impairment (CrCl <70 ml/min). Slowly taper to discontinuation to prevent withdrawal seizures	Almost exclusively eliminated renally. Dose should be modified in patients with renal impairment	Excreted primarily through the kidneys. Dose modifications may be necessary in individuals with renal impairment. Slowly taper to discontinuation to prevent withdrawal

consumption and binge drinking [51]. There is also evidence from one trial that a combination of gabapentin and naltrexone in the first 6 weeks after drinking cessation performed better than naltrexone alone at preventing relapse to heavy drinking [52]. However, a large multicenter alcohol use disorder trial investigating gabapentin enacarbil extended-release, a longer-acting prodrug formulation of gabapentin, showed no effect on any drinking outcome measure [53]. Gabapentin has been demonstrated to have some potential for abuse [54], so adherence with the prescribed dosage should be closely monitored.

- Baclofen is a selective $GABA_B$ receptor agonist that is FDA-approved for the treatment of spasticity associated with multiple sclerosis and spinal cord diseases. Baclofen is frequently used in some European countries as an off-label medication for alcohol use disorder. However, the evidence for baclofen's efficacy on alcohol use disorder treatment is mixed [55]. Although some physicians prescribe baclofen to patients who are actively drinking, there is an increased risk of side effects in individuals who consume alcohol while taking baclofen and most trials have tested baclofen in abstinent patients [56].

Review Questions

1. A 61-year-old man presents to the emergency room following a witnessed seizure. He typically consumes approximately 20 standard drinks per day, but reports that he has abstained from alcohol for the past day and a half. The attending physician believes this may be an alcohol withdrawal seizure. Which of the following is correct regarding his condition?
   A. Withdrawal seizures usually require long-term antiepileptic medications.
   B. Withdrawal seizures may progress to delirium tremens in nearly one-third of the population.
   C. Phenytoin, carbamazepine, and levetiracetam are first-line treatments.
   D. Withdrawal seizures typically occur about 96 hours after the last alcoholic drink.
   E. Withdrawal seizures are usually partial complex seizures.

   Answer: B.

   Explanation: Left untreated, alcohol withdrawal seizures may progress to delirium tremens in nearly one-third of the population. Withdrawal seizures are typically generalized tonic-clonic seizures that occur within 6 to 48 hours after the last alcoholic drink. Withdrawal seizures should be treated with benzodiazepines. They are usually self-limited and do not require long-term treatment with antiepileptics.
2. A neuroscience major with a history of occasional binge drinking presents to your office at a local student health center. She asks about the acute effects of ethanol on the brain. As part of your explanation, which of the following would you tell her about the effects of alcohol on excitatory and inhibitory neurotransmission?
   A. Acute consumption decreases activity at both $GABA_A$ receptors and NMDA receptors.
   B. Acute consumption decreases activity at $GABA_A$ receptors and increases activity at NMDA receptors.
   C. Acute consumption increases activity at $GABA_A$ receptors and decreases activity at NMDA receptors.
   D. Acute consumption increases activity at both $GABA_A$ receptors and NMDA receptors.
   E. Acute consumption has no effect at $GABA_A$ receptors and NMDA receptors.

Answer: C.

Explanation: Acute alcohol intake increases $GABA_A$ activity through direct effects on the receptor and indirect effects such as increased presynaptic GABA release. NMDA receptors are typically inhibited by acute ingestion of ethanol.

3. A 44-year-old woman is referred to your clinic for management of her alcohol use disorder. She has previously been treated with naltrexone and acamprosate, but neither of these medications has had any discernable effect on her drinking. You are considering treating her with disulfiram, but are aware that disulfiram has multiple contraindications and potential side effects. While explaining the risks of this medication, you should inform her that:
   A. She should abstain from alcohol for 6 hours prior to initiating treatment with disulfiram.
   B. Mild metabolic acidosis is a common side effect.
   C. Withdrawal seizures may occur if disulfiram is stopped suddenly.
   D. Disulfiram-ethanol reactions can occur up to 30 days after the last use of disulfiram.
   E. Optic neuritis is a rare but serious side effect.

Answer: E.

Explanation: Optic neuritis, peripheral neuropathy, psychosis, and hepatotoxicity are rare but serious side effects of disulfiram use. Patients must abstain from alcohol for over 12 hours prior to the initiation of disulfiram. Patients should avoid products containing alcohol and be notified that disulfiram-ethanol reactions can occur up to 14 days after the last use of disulfiram. Metabolic acidosis may occur with topiramate treatment, not disulfiram treatment. Withdrawal seizures can occur when either topiramate or baclofen are stopped suddenly, these medications need to be tapered to discontinuation.

4. A 22-year-old patient has been in treatment at an inpatient recovery center for the past 6 days. He was intoxicated upon admission and prior to treatment had been consuming roughly 10 standard drinks per day for the past 6 weeks. He has no other health conditions. Which of the following biomarker profiles is most likely for this patient at this point in recovery?

	Ethyl glucuronide (EtG)	Phosphatidylethanol (PEth)	Gamma-glutamyltransferase (GGT)	Carbohydrate-deficient transferrin (%CDT)
A.	Negative	Positive	Elevated	Elevated
B.	Positive	Positive	Elevated	Elevated
C.	Negative	Negative	Normal	Normal
D.	Positive	Negative	Elevated	Elevated
E.	Positive	Positive	Normal	Normal

Answer: A.

Explanation: Ethyl glucuronide (EtG) is a direct biomarker that is most likely to test positive 24 hours after alcohol consumption, but can remain positive for up to 5 days following heavy consumption. Since this patient has not consumed

alcohol for 6 days, his urine EtG will likely be negative. Phosphatidylethanol (PEth) may still test positive after 6 days and can remain detectable in whole blood for up to 2 weeks following heavy consumption. Gamma glutamyltransferase (GGT) may be elevated after several weeks of heavy drinking and typically returns to normal after 2–6 weeks of abstinence. Carbohydrate-deficient transferrin (CDT) levels are elevated following consumption of 60–80 grams of alcohol per day for 2–3 weeks and return to normal after 2–4 weeks of abstinence and would therefore likely be elevated in this patient.

References

1. Stanaway JD, Afshin A, Gakidou E, Lim SS, Abate D, Abate KH, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet (London, England). 2018;392(10159):1923–94.
2. Xu J, Murphy S, Kochanek K, Bastian B, Arias E. Deaths: final data for 2016. National vital statistics reports: from the Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System. 2018;67(5):1.
3. QuickStats: age-adjusted death rates∗ attributable to alcohol-induced causes,(dagger) by race/ethnicity – United States, 1999–2015. MMWR Morb Mortal Wkly Rep. 2017;66(18):491.
4. Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, et al. Epidemiology of DSM-5 alcohol use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA Psychiat. 2015;72(8):757–66.
5. Grant BF, Chou SP, Saha TD, Pickering RP, Kerridge BT, Ruan WJ, et al. Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001-2002 to 2012-2013: results from the National Epidemiologic Survey on Alcohol and Related Conditions. JAMA Psychiat. 2017;74(9):911–23.
6. Hasin DS, Stinson FS, Ogburn E, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry. 2007;64(7):830–42.
7. Tan CH, Denny CH, Cheal NE, Sniezek JE, Kanny D. Alcohol use and binge drinking among women of childbearing age – United States, 2011–2013. MMWR Morb Mortal Wkly Rep. 2015;64(37):1042–6.
8. Brady KT, Randall CL. Gender differences in substance use disorders. Psychiatr Clin North Am. 1999;22(2):241–52.
9. Kanny D, Naimi TS, Liu Y, Lu H, Brewer RD. Annual total binge drinks consumed by U.S. adults, 2015. Am J Prev Med. 2018;54(4):486–96.
10. Grant BF, Dawson DA. Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. J Subst Abus. 1997;9:103–10.
11. Leggio L, Kenna GA, Fenton M, Bonenfant E, Swift RM. Typologies of alcohol dependence. From Jellinek to genetics and beyond. Neuropsychol Rev. 2009;19(1):115–29.
12. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.
13. Gowin JL, Sloan ME, Stangl BL, Vatsalya V, Ramchandani VA. Vulnerability for alcohol use disorder and rate of alcohol consumption. Am J Psychiatry. 2017;174(11):1094–101.
14. Verhulst B, Neale MC, Kendler KS. The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. Psychol Med. 2015;45(5):1061–72.

15. Edenberg HJ, McClintick JN. Alcohol dehydrogenases, aldehyde dehydrogenases, and alcohol use disorders: a critical review. Alcohol Clin Exp Res. 2018;42(12):2281–97.
16. Walters RK, Polimanti R, Johnson EC, McClintick JN, Adams MJ, Adkins AE, et al. Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. Nat Neurosci. 2018;21(12):1656–69.
17. Li D, Zhao H, Gelernter J. Strong association of the alcohol dehydrogenase 1B gene (ADH1B) with alcohol dependence and alcohol-induced medical diseases. Biol Psychiatry. 2011;70(6):504–12.
18. Tawa EA, Hall SD, Lohoff FW. Overview of the genetics of alcohol use disorder. Alcohol Alcohol (Oxford, Oxfordshire). 2016;51(5):507–14.
19. Brooks PJ, Enoch MA, Goldman D, Li TK, Yokoyama A. The alcohol flushing response: an unrecognized risk factor for esophageal cancer from alcohol consumption. PLoS Med. 2009;6(3):e50.
20. Cederbaum AI. Alcohol metabolism. Clin Liver Dis. 2012;16(4):667–85.
21. National Institute on Alcohol Abuse and Alcoholism. Alcohol alert: alcohol metabolism. No. 35, PH 371. Bethesda: The Institute; 1997.
22. Hernandez-Munoz R, Caballeria J, Baraona E, Uppal R, Greenstein R, Lieber CS. Human gastric alcohol dehydrogenase: its inhibition by H2-receptor antagonists, and its effect on the bioavailability of ethanol. Alcohol Clin Exp Res. 1990;14(6):946–50.
23. Kumar S, Porcu P, Werner DF, Matthews DB, Diaz-Granados JL, Helfand RS, et al. The role of GABA(A) receptors in the acute and chronic effects of ethanol: a decade of progress. Psychopharmacology. 2009;205(4):529–64.
24. Lovinger DM, White G, Weight FF. Ethanol inhibits NMDA-activated ion current in hippocampal neurons. Science. 1989;243(4899):1721–4.
25. Gass JT, Olive MF. Glutamatergic substrates of drug addiction and alcoholism. Biochem Pharmacol. 2008;75(1):218–65.
26. Vonghia L, Leggio L, Ferrulli A, Bertini M, Gasbarrini G, Addolorato G. Acute alcohol intoxication. Eur J Intern Med. 2008;19(8):561–7.
27. National Institute on Alcohol Abuse and Alcoholism. Understanding the Dangers of Alcohol Overdose 2018. Available from: https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/understanding-dangers-of-alcohol-overdose.
28. Jung YC, Namkoong K. Alcohol: intoxication and poisoning – diagnosis and treatment. Handb Clin Neurol. 2014;125:115–21.
29. Marco CA, Kelen GD. Acute intoxication. Emerg Med Clin North Am. 1990;8(4):731–48.
30. Allison MG, McCurdy MT. Alcoholic metabolic emergencies. Emerg Med Clin North Am. 2014;32(2):293–301.
31. Center for Substance Abuse Treatment. Detoxification and Substance Abuse Treatment. Treatment Improvement Protocol (TIP) Series, No. 45. HHS publication no. (SMA) 15-4131. Rockville: Center for Substance Abuse Treatment; 2006.
32. Bayard M, McIntyre J, Hill KR, Woodside J Jr. Alcohol withdrawal syndrome. Am Fam Physician. 2004;69(6):1443–50.
33. Rathlev NK, Ulrich AS, Delanty N, D'Onofrio G. Alcohol-related seizures. J Emerg Med. 2006;31(2):157–63.
34. Tovar R. Diagnosis and treatment of alcohol withdrawal. JCOM. 2011;18(8):361–70.
35. Schuckit MA. Recognition and management of withdrawal delirium (delirium tremens). N Engl J Med. 2014;371(22):2109–13.
36. Mayo-Smith MF, Beecher LH, Fischer TL, Gorelick DA, Guillaume JL, Hill A, et al. Management of alcohol withdrawal delirium. An evidence-based practice guideline. Arch Intern Med. 2004;164(13):1405–12.
37. Helander A, Bottcher M, Fehr C, Dahmen N, Beck O. Detection times for urinary ethyl glucuronide and ethyl sulfate in heavy drinkers during alcohol detoxification. Alcohol Alcohol. 2009;44(1):55–61.

38. Jatlow PI, Agro A, Wu R, Nadim H, Toll BA, Ralevski E, et al. Ethyl glucuronide and ethyl sulfate assays in clinical trials, interpretation, and limitations: results of a dose ranging alcohol challenge study and 2 clinical trials. Alcohol Clin Exp Res. 2014;38(7):2056–65.
39. Wojcik MH, Hawthorne JS. Sensitivity of commercial ethyl glucuronide (ETG) testing in screening for alcohol abstinence. Alcohol Alcohol (Oxford, Oxfordshire). 2007;42(4):317–20.
40. Hansson P, Caron M, Johnson G, Gustavsson L, Alling C. Blood phosphatidylethanol as a marker of alcohol abuse: levels in alcoholic males during withdrawal. Alcohol Clin Exp Res. 1997;21(1):108–10.
41. Allen JP, Sillanaukee P, Strid N, Litten RZ. In: Allen JP, Wilson VB, editors. Biomarkers of heavy drinking. Bethesda: U.S. Department of Health and Human Services; 2003. p. 37–53.
42. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The alcohol use disorders identification test. Guidelines for use in primary health care. Geneva: World Health Organization; 1992.
43. Mayfield D, McLeod G, Hall P. The CAGE questionnaire: validation of a new alcoholism screening instrument. Am J Psychiatry. 1974;131(10):1121–3.
44. Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA. 2006;295(17):2003–17.
45. Kranzler HR, Soyka M. Diagnosis and pharmacotherapy of alcohol use disorder: a review. JAMA. 2018;320(8):815–24.
46. Center for Substance Abuse Treatment. Incorporating alcohol pharmacotherapies into medical practice. Treatment Improvement Protocol (TIP) series 49. HHS publication no. (SMA) 09-4380. Substance Abuse and Mental Health Services Administration: Rockville; 2009.
47. Skinner MD, Lahmek P, Pham H, Aubin HJ. Disulfiram efficacy in the treatment of alcohol dependence: a meta-analysis. PLoS One. 2014;9(2):e87366.
48. Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA. 2014;311(18):1889–900.
49. Kalk NJ, Lingford-Hughes AR. The clinical pharmacology of acamprosate. Br J Clin Pharmacol. 2014;77(2):315–23.
50. Kenna GA, Lomastro TL, Schiesl A, Leggio L, Swift RM. Review of topiramate: an antiepileptic for the treatment of alcohol dependence. Curr Drug Abuse Rev. 2009;2(2):135–42.
51. Mason BJ, Quello S, Shadan F. Gabapentin for the treatment of alcohol use disorder. Expert Opin Investig Drugs. 2018;27(1):113–24.
52. Anton RF, Myrick H, Wright TM, Latham PK, Baros AM, Waid LR, et al. Gabapentin combined with naltrexone for the treatment of alcohol dependence. Am J Psychiatry. 2011;168(7):709–17.
53. Falk DE, Ryan ML, Fertig JB, Devine EG, Cruz R, Brown ES, et al. Gabapentin Enacarbil extended-release for alcohol use disorder: a randomized, double-blind, placebo-controlled, multisite trial assessing efficacy and safety. Alcohol Clin Exp Res. 2019;43(1):158–69.
54. Evoy KE, Morrison MD, Saklad SR. Abuse and misuse of Pregabalin and gabapentin. Drugs. 2017;77(4):403–26.
55. de Beaurepaire R, Sinclair JMA, Heydtmann M, Addolorato G, Aubin HJ, Beraha EM, et al. The use of baclofen as a treatment for alcohol use disorder: a clinical practice perspective. Front Psych. 2018;9:708.
56. Agabio R, Sinclair JM, Addolorato G, Aubin HJ, Beraha EM, Caputo F, et al. Baclofen for the treatment of alcohol use disorder: the Cagliari statement. Lancet Psychiatry. 2018;5(12):957–60.

Benzodiazepines and Other Sedatives, Hypnotics, and Anxiolytics

9

Christine LaGrotta and Anil Thomas

High-Yield Review Points

- The incidence of benzodiazepine use, both prescribed and non-prescribed, has been increasing in the past two decades, and the risk of interaction between opioids and benzodiazepines is becoming more important because of concerns about high rates of concurrent use, synergistic effects with concurrent use, and high rates of concurrent use in fatal opioid overdoses.
- Sedative, hypnotic, and anxiolytic intoxication must be evaluated to determine risk for toxicity, overdose, and withdrawal complications, as well as assessing for other causes of altered mental status such as co-ingestion with additional CNS depressants.
- Withdrawal from sedatives, hypnotics, and anxiolytics is a medical emergency that can lead to seizures and death.
- Barbiturates, though less commonly prescribed than benzodiazepines, have a narrower therapeutic index and are more lethal in overdose than other sedative-hypnotics.
- Benzodiazepine derivatives, also called nonbenzodiazepine "z"-drugs, are commonly prescribed for insomnia, though have many adverse effects that need to be recognized by clinicians, such as hallucinations, amnesia, parasomnias, coma, and death.

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Epidemiology

The 2017 National Survey on Drug Use and Health showed the incidence of tranquilizer use disorder in the United States was 0.6% of people aged 12 and older, representing about 1.7 million people [1]. Between 1996 and 2013, the percentage of adults filling a benzodiazepine prescription increased from 4.1% to 5.6% with an annual percentage change of 2.5%. During that time period (1996–2013), the overdose rate increased from 0.58 to 3.07 per 100,000 adults (with a plateau from 2010 onward) [2]. Another study showed that among US adults, between 2015 and 2016, 12.5% of the population used benzodiazepines, 2.1% misused benzodiazepines at least once, and 0.2% had a benzodiazepine use disorder [3].

In the past few years, especially with the current increased problems with opioids, even more attention is being given to benzodiazepines because of concerns about high rates of concurrent use, synergistic effects with concurrent use, and high rates of concurrent use in fatal opioid overdoses. Non-medical benzodiazepine use is common in those with opioid use disorder, which is concerning because of the risk for overdose when opioid and benzodiazepines are combined. The number of deaths involving benzodiazepines, in combination with other synthetic narcotics, has been steadily increasing since 2014, while the number of deaths involving benzodiazepines without any opioids has remained steady. Between 2007 and 2017 there was a 1.7-fold increase in deaths involving benzodiazepines only, while there was a 2.8-fold increase in deaths involving benzodiazepine and any opioids and an 11.2-fold increase in death involving benzodiazepines and other synthetic narcotics [4]. A study in 2017 by McHugh et al. suggested a potential explanation for the co-occurring nonmedical use of benzodiazepines and opioids: nonmedical use of these medications might help reduce anxiety, sleep disruption, or an acute protracted withdrawal [5].

Risk Factors

The main risk factors for diagnosis of a benzodiazepine use disorder include participation in a self-help group for medication dependence, younger age, longer duration of benzodiazepine use, higher dose of benzodiazepine, the interaction of higher benzodiazepine dose with longer duration of benzodiazepine use, lower level of education, non-native cultural origin and outpatient treatment for alcohol and/or drug dependence. Less predictive risk factors are a short benzodiazepine half-life and higher levels of depression and anxiety [6].

Mechanism of Action

Benzodiazepines, as well as barbiturates and "Z-drugs," work on the gamma-amino butyric acid (GABA) system in the body. GABA is synthesized by the neurotransmitter glutamate and is the primary inhibitory neurotransmitter in both the brain and

spinal cord. There are three different types of GABA receptors: two ionotropic (GABA-A and GABA-C) and one metabotropic, G-protein-coupled receptor (GABA-B). When GABA binds the ionotropic receptor, ion channels open and an influx of negative chloride (Cl-) ions results in inhibition of the neuron. Benzodiazepines, barbiturates, and alcohol all bind GABA-A receptors. Benzodiazepines act as positive allosteric modulators at the GABA-A receptor, specifically binding in a pocket created by the alpha and gamma subunits, thus causing a conformational change that allows GABA to bind. There are two benzodiazepine receptor subunits: benzodiazepine subunit 1 (BZD1) and benzodiazepine subunit 2 (BZD2). BZD1 receptors are highly concentrated in the cortex, thalamus, and cerebellum and are responsible for the sedative effects and anterograde amnesia caused by benzodiazepines. BZD2 receptors are highly concentrated in the limbic system, motor neurons and dorsal horn of the spinal cord and are responsible for the anxiolytic effects of benzodiazepines [7].

Benzodiazepines increase the *frequency* of GABA-A receptor openings, while barbiturates increase the *duration* of opening, both resulting in an increase in Cl- ions into the neuron, causing further inhibition. GABA-B receptors are thought to be important in pain, mood, and memory, while the function of GABA-C receptors is not known. With chronic exposure to benzodiazepines, there is both a decreased GABA-A receptor response as well as a change in the expression of this receptor subtype. Because of this, there is less of an inhibitory response and physical dependence emerges. With chronic exposure there is an increased expression of excitatory glutamatergic neurons upon withdrawal, which may lead to some of the clinical symptoms of benzodiazepine withdrawal (see below).

Similar to other substances of abuse, benzodiazepines increase dopamine (DA) in the mesolimbic dopaminergic system. The ventral tegmental area (VTA) contains GABA interneurons (as well as glutamate and dopamine neurons). When benzodiazepines bind to the GABA interneurons, the neurons are hyperpolarized, and then no longer inhibit DA neurons. Since GABA is inhibitory, there is subsequently more dopamine released (less inhibition).

Pharmacokinetics

The onset and duration of action of benzodiazepines is largely determined by three factors: half-life, rate of absorption, and lipophilicity. Half-life is determined by how the drug is metabolized and the presence of active metabolites. The greater the lipophilicity of a drug, the quicker it crosses the blood–brain barrier, causing a more rapid effect. Using these factors, benzodiazepines can be divided into three categories: short acting (15–30 min), intermediate acting (30–60 min), and long acting (1+ hours). See Table 9.1 for the characteristics of common benzodiazepines.

Table 9.1 Pharmacology of commonly used benzodiazepines [8, 9]

Drug	Relative potency (mg)	Onset of action[a]	Peak onset (hours)	Elimination half-life[b] (hours)
Alprazolam	0.5	Intermediate	0.5–1.5	6–20[c]
Chlordiazepoxide	10	Intermediate	2-4	3–100
Clonazepam	0.25–0.5	Intermediate	1–4	18–40
Diazepam	5	Rapid	0.5–1	40–120[d]
Lorazepam	1	Intermediate	2-4	10–20
Oxazepam	15	Slow	2–3	5–20

[a]Rapid = 15 min, Intermediate =15–30 min, Slow = 30–60 min
[b]Includes metabolites
[c]Varies with age, hepatic functioning, and weight
[d]Increased in older age, renal, or hepatic impairment

Diagnosis

Diagnosis of a use disorder is made using DSM-5 criteria under the heading of Sedative, Hypnotic, or Anxiolytic Use Disorder. As with other substances, the severity of the use disorder is classified based on a number of criteria met. The criteria are the same as other substance use disorders and as reported elsewhere in this book. The diagnosis for intoxication and withdrawal is discussed below.

Intoxication

Clinical Syndrome

According to the DSM-5, signs of benzodiazepine intoxication include one or more of the following (developing during or shortly after use): slurred speech, incoordination, unsteady gait, nystagmus, impairment in cognition (attention or memory), and stupor or coma. The impairment in memory that occurs during intoxication is most often characterized by an anterograde amnesia that resembles an "alcoholic blackout." [10]

Overdose

Benzodiazepine overdose most commonly presents as CNS depression with normal vital signs, and the patient is often able to provide a history. Benzodiazepines have a relatively large therapeutic index and thus on their own overdoses will usually only exhibit only mild CNS symptoms [11]. There is often co-ingestion with other

substances, most often alcohol. Respiratory compromise is unlikely, unless co-ingestion with another depressant has occurred (alcohol or opioids commonly). Respiratory compromise also depends on other factors, such as tolerance, weight, age, and genetics. The clinical presentation is similar to other depressants including ethanol, barbiturates, gamma hydroxybutyrate (GHB), and chloral hydrate. A differential diagnosis of benzodiazepine overdose can include other substances, hypoglycemia, carbon monoxide poisoning, stroke, meningitis, and encephalitis. The workup should include glucose levels, acetaminophen and salicylate levels, a pregnancy test, an EKG and ethanol levels. Head CT and cerebrospinal analysis should be considered if clinically indicated.

Laboratory/Diagnostic Evaluation

Urine immunoassay drug screens typically not detect for the parent compound, rather they test for metabolites like nordiazepam and oxazepam. Oxazepam is a metabolite of diazepam, temazepam, and chlordiazepoxide. Other benzodiazepines have a low cross-reactivity in the immunoassay, so that a number of routinely ingested benzodiazepines are often missed if taken in low doses, including clonazepam, lorazepam, alprazolam, or midazolam. Immunoassays used can vary across labs, and may have different cross-reactants. False negatives can occur due to limited cross-reactivity, but false positives can occur with medications like sertraline [12].

Treatment

Treatment in intoxication starts with stabilization of the airway, breathing, and circulation. Once the diagnosis of benzodiazepine overdose or intoxication is established, targeted treatment can occur. Using activated charcoal as a gastrointestinal decontaminant is not recommended due to increased risk of aspiration. Flumazenil is a specific and competitive antagonist at the benzodiazepine receptor that reverses the effects of agonists. It is given as 0.1 to 0.3 mg IV over 30 seconds. This dose can be repeated if necessary. Usually, response will occur with doses <1.0 mg in pure benzodiazepine overdose and < 2.0 mg in a mixed overdose. Due to the short half-life of flumazenil, re-sedation may occur after administration, requiring re-administration. Controversy exists over the use of flumazenil in clinical situations, particularly in those with a history of seizures or who were given benzodiazepines for seizure control, as it can precipitate seizures in those with benzodiazepine tolerance. Caution should be used if a patient's EKG is indicative of tricyclic antidepressant overdose, in patients taking drugs that could cause seizures in overdose, and in patients taking MAOI's, lithium, and arrhythmogenic drugs [13].

Withdrawal

Clinical Syndrome

Individuals can become tolerant to benzodiazepines in a few weeks, and physical dependence can occur quickly, putting the person at risk for withdrawal. Benzodiazepine withdrawal is named in the DSM-5 as Sedative, Hypnotic, or Anxiolytic Withdrawal and is defined as cessation in (or reduction in) sedative, hypnotic, or anxiolytic use that has been prolonged. Two or more of the following must be present: (1) autonomic hyperactivity (e.g., sweating or pulse rate > 100 bpm), (2) hand tremor, (3) insomnia, (4) nausea or vomiting, (5) transient visual, tactile, or auditory hallucinations or illusions, (6) psychomotor agitation, (7) anxiety, and (8) grand mal seizures [10].

Though the DSM-5 lists the eight symptoms above, this is not an exhaustive list. Withdrawal symptoms can be divided into psychological and physical. Psychological symptoms can include increased anxiety, excitability, insomnia and nightmares, panic attacks and agoraphobia, social phobia, perceptual distortions, depersonalization, derealization, hallucinations, misperceptions, depression, obsessions, paranoid thoughts, irritability, and poor memory and concentration. Physical symptoms can include headache, body pain/stiffness, seizure, tingling, numbness, altered sensation, weakness, fatigue, influenza-like symptoms, muscle twitches, jerks, tics, electric shock-like sensations, tremor, dizziness, lightheadedness, tinnitus, hypersensitivity (to light, sounds, tough, taste and smell), gastrointestinal symptoms (nausea, vomiting, diarrhea, constipation, pain, distension, difficulty swallowing), appetite or weight change, dry mouth, and metallic taste or an unusual smell [14].

Treatment

The mainstay for treatment of benzodiazepine withdrawal is to use benzodiazepines themselves to help control withdrawal symptoms. The goal is to eliminate withdrawal symptoms without causing excessive sedation or respiratory depression. A Cochrane systematic review noted that when withdrawing or tapering a person from benzodiazepines, a longer withdrawal (10 weeks) was preferred to a shorter time period because of a higher dropout rate in those being tapered too quickly. This specific review did not find much benefit in switching from a short-acting to a long-acting benzodiazepine. There was no evidence to support the use of propranolol, buspirone, progesterone, or hydroxyzine in terms of managing benzodiazepine withdrawal or improving abstinence. There was some evidence that carbamazepine might have been used as an adjunctive medication for benzodiazepine withdrawal, especially in individuals receiving the equivalent of 20 mg/day or more of diazepam [15].

Barbiturates

Mechanism of Action

Barbiturates, similarly to benzodiazepines, have action at the GABA-A receptor. However, barbiturates increase the *duration* of opening of the GABA receptors while benzodiazepines increase the *frequency* of opening of the GABA receptors. In general, the barbiturates are well absorbed after oral administration. They are metabolized by the liver and excreted by the kidneys. The half-lives range from 1 to 120 hours.

Clinical Uses

Barbiturates are used less in the clinical setting since the development and increased popularity of benzodiazepines and other hypnotics. However, they still have some use in clinical practice. The barbiturate methohexital is used as an anesthetic agent for ECT as well as to abort prolonged seizures in ECT, or to limit postictal agitation. Phenobarbital is the most commonly used barbiturate for the treatment of seizures (including status epilepticus, generalized tonic-clonic, and simple partial seizures). Butalbitol is one ingredient in the pain medication Fioricet. The barbiturate amobarbital has historically been used to help in diagnosis of different psychiatric conditions such as conversion disorder, catatonia, and unexplained muteness. On occasion, barbiturates can also be used for sleep as they reduce sleep latency and the number of awakenings per night. They are rarely used, however, as tolerance to these effects usually develops in about 2 weeks and discontinuation of the barbiturates can lead to rebound worsening of insomnia [16].

Adverse Effects

Barbiturates and benzodiazepines have many overlapping adverse effects. However, there are some that are more specific to barbiturates. These can include the development of Stevens-Johnson syndrome, megaloblastic anemia, and neutropenia. Barbiturates can also precipitate acute porphyria reactions. One of the biggest differences between benzodiazepines and barbiturates is the low therapeutic index of barbiturates, making fatal overdose more likely [16].

Intoxication with barbiturates is similar to that of benzodiazepines and includes delirium, confusion, and CNS and respiratory depression. Respiratory depression is more likely when there is co-ingestion of another CNS depressant.

Treatment

The treatment of barbiturate intoxication, withdrawal, and barbiturate use disorders are similar to that of benzodiazepines. There are several instances in which the treatment of the two differs.

Intoxication: As stated above, barbiturates have a narrower therapeutic index than benzodiazepines and so in treatment of acute intoxication, care must be taken to be even more vigilant to assess airway, breathing, and circulation. In addition, since flumazenil binds to the benzodiazepine receptor, it will not reverse the effects of a barbiturate overdose [17].

Withdrawal: Treatment of withdrawal from barbiturates is similar to that of benzodiazepines. Though barbiturates can be used to treat withdrawal, because of the narrow therapeutic index, benzodiazepines are often used in a similar fashion to treatment of benzodiazepine withdrawal.

Barbiturate Use Disorder: Falling also under the DSM-5 classification of Sedative, Hypnotic, or Anxiolytic Use Disorders, treatment is both pharmacologically and psychosocially similar to that of benzodiazepine use disorder.

Benzodiazepine Derivatives/"Z"-Drugs

Other sedative-hypnotics include the nonbenzodiazepine sleeping agents, more commonly referred to as "z" drugs. The most common of these drugs are zolpidem (Ambien), eszopiclone (Lunesta), and zaleplon (Sonata). These drugs are thought to also work at the GABA-A receptor, though they selectively have a high affinity for the alpha-1 hypnotic-inducing site on the benzodiazepine subunit on the GABA-A receptor. They were introduced into the market in the 1990s and have only been approved for insomnia.

Pharmacology

Zolpidem is an imidazopyridine agent that acts mainly on the alpha-1 GABA-A receptor, with minimal effect on the alpha 2, 3, and 5 subunits. It is considered a potent sedative-hypnotic with little anxiolytic efficacy. The standard dose of the immediate release form (most commonly prescribed) is 10 mg in men and 5 mg in women (due to a recommendation from the FDA in 2013 stemming from increased duration of action in women), and a lower dose should be considered in the elderly. It is available in both an immediate-release and an extended-release preparation. It is metabolized by the CYP450 system (predominantly CYP3A4), thus requiring a lower dose in those with hepatic impairment [18].

Table 9.2 Pharmacology of commonly used "Z-drugs" [18–21]

Generic name	Main clinical effect	Time to onset of effects	Half-life	Maximum daily dose
Zolpidem IR	Sleep initiation	1.6 hours	1.4 to 4.5 hours	5 mg for females 10 mg for males
Zolpidem ER	Sleep initiation and sleep maintenance	1.5 hours	1.4 to 4.5 hours	6.25 mg for females 12.5 mg for males
Eszopiclone	Sleep initiation and sleep maintenance	~1 hour	~6 hours	3 mg
Zaleplon	Sleep initiation	~1 hour	~1 hour	20 mg

Eszopiclone is a cyclopyrrolone drug that is the s-enantiomer of the racemic mixture zopiclone (only eszopiclone is available in the United States). Eszopiclone has affinity for the alpha 2 and 3 subunits at the GABA-A receptor. Note that zopiclone requires dose reduction in those with renal impairment, though there is not the same recommendation for eszopiclone [18]. Zaleplon is a pyrazolopyrimidine drug that exerts its effects by selectively binding to the alpha-1 subunit of the (BZ1) receptor with low affinity at the alpha 2 and 3 subunits. It is short acting, which gives it the benefit of being able to be taken after trying to fall asleep or for middle of the night awakening. It is not useful in sleep maintenance. It has low bioavailability due to extensive first-pass hepatic metabolism and thus dosage decrease is recommended in patients with hepatic impairment [18]. See Table 9.2 for the pharmacology of commonly used "Z-drugs."

Adverse Effects

The most common adverse effects of the "z"-drugs are headache, GI distress, and dizziness, though they are generally well tolerated. Ten to thirty-five percent of people taking zopiclone/eszopiclone noted a bitter or unpleasant taste that was bad enough to lead to cessation of the drug. All 3 drugs are on a list that was released by the FDA in 2007 as having a potential risk of increased sleep-related behaviors such as eating or driving while sleeping (this is especially prominent with zolpidem). Daytime residual effects on cognition and psychomotor performance are a concern. They have an effect on next day performance of body balance, reaction times, and ability to multitask [18].

There is also a concern for tolerance, dependence, and withdrawal from all of the "z"-drugs, however this appears to be less common and less severe than with benzodiazepines. After cessation of the drug, especially higher doses of zolpidem, rebound insomnia can occur. The withdrawal from the drugs is similar to the withdrawal from other benzodiazepines and includes insomnia, delirium, craving, anxiety, tremor, palpitations, and rarely, seizures and psychosis [18].

Review Question #1

A 56-year-old female presents to her primary care doctor having good benefit for initiating sleep with diazepam, but finds that she feels groggy the next day. The duration of action of a benzodiazepine is based on which of the following:

A. The drug itself
B. The drug itself and its active metabolites
C. The drug itself and inactive metabolites
D. The drug itself and all metabolites, both active and inactive
E. Only the drug's active metabolites

Answer: B. The drug itself and its active metabolites.

Explanation: The duration of action of a benzodiazepine is based on the drug itself and its active metabolites. Inactive metabolites do not have clinical effect, and thus do not contribute to the duration of action of the benzodiazepine.

Reference: Sankar [22].

Review Question #2

An 8-year-old female with no medical history presents to the emergency room after finding her mother's lorazepam and taking what was left in the bottle. She requires the administration of flumazenil due to excessive somnolence. Which of the following is true of flumazenil?

A. It is metabolized by the kidney
B. There are no scales that can be used to monitor the effect of flumazenil
C. Once awoken with flumazenil, there is no need for readministration
D. If there is a suspected co-ingestion with opioids, naloxone should be given prior to flumazenil
E. Flumazenil can be given without consideration for a history of seizures

Answer: D.

Explanation: If there is a suspected co-ingestion with opioids, naloxone should be given prior to flumazenil as it is better tolerated and has a better safety profile. Flumazenil is metabolized by the liver. The Glasgow coma scale can be used to monitor the effects of flumazenil. Flumazenil has a short duration of action, and may need to be readministered. History of seizures should be considered before giving flumazenil in patients, particularly those with benzodiazepine dependence who are at risk for withdrawal seizures.

Reference: Weinbroum et al. [13]

Review Question #3

A 34-year-old man with insomnia asks a friend for medication to help sleep. He takes the medication, unaware of what he is taking, and experiences side effects. Which of the following is a possible adverse effect of barbiturate use?

A. Cough suppression
B. Stevens-Johnson syndrome
C. Loss of appetite
D. Constipation
E. Increased immune response

Answer: B.

Explanation: Stevens-Johnson syndrome is an adverse effect of barbiturate use; others include development of acute intermittent porphyria attacks, neutropenia, and megaloblastic anemia. The other answers are not adverse effects of barbiturate use.

Reference: Sadock and Sadock [16].

Review Question #4

A 30-year-old medical student comes into the clinic requesting a short-term medication for anxiety for an upcoming flight overseas and is prescribed clonazepam. She asks her doctor about the mechanism of action of the medication she is given. The binding of benzodiazepines and barbiturates to the GABA-A receptor allow for the influx of which of the following:

A. Sodium
B. Chloride
C. Bicarbonate
D. Potassium
E. Glutamate

Answer: B.

Explanation: The binding of benzodiazepines and barbiturates to the GABA-A receptor allows for the influx of negatively charged chloride ions. The other answers are simply distractors.

Reference: Twyman et al. [23].

Review Question #5

Which of the following is a correct statement regarding benzodiazepines and barbiturates and the receptors they act upon?

A. Barbiturates have a more dangerous withdrawal syndrome because of their binding to the GABA-C receptor
B. Barbiturates bind to the GABA-B receptor
C. The alpha-1 subunit of the GABA-A receptor mediates sleep
D. Benzodiazepines are less safe in overdose compared to barbiturates
E. There is no cross-tolerance between barbiturates and benzodiazepines

Answer C.

Explanation: It is the alpha-1 subunit of the GABA-A receptor that is involved in mediating sleep (which is why the nonbenzodiazepine "Z-drugs" that act on the alpha-1 subunit are involved in promoting sleep). Barbiturates do have a dangerous withdrawal syndrome but they act on the GABA-A receptor, making answer choices a and b incorrect. Barbiturates are more dangerous in overdose compared to benzodiazepines and there is cross-tolerance between barbiturates and benzodiazepines.

Reference: Sadock and Sadock [16].

Review Question #6

A 72-year-old female who was overusing her daughter's prescribed lorazepam recently stopped using it at the urging of her physician. According to the DSM-V, for how long should a person **not** meet any criteria for sedative, hypnotic, or anxiolytic use disorder (except for craving) in order to be considered in early remission?

A. As soon as they stop using the substance
B. 2 weeks
C. 1 month
D. 3 months
E. 12 months

Answer D.

Explanation: This is a definition question from the DSM. Early remission is defined as at least 3 months.

Reference: American Psychiatric Association [10].

References

1. McCance-Katz EF. The national survey on drug use and health. Substance Abuse and Mental Health Services Administration. 2017. https://www.samhsa.gov/data/sites/default/files/nsduh-ppt-09-2018.pdf.
2. Bachhuber MA, Hennessy S, Cunningham CO, Starrels JL. Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996–2013. Am J Public Health. 2016;106(4):686–8.
3. Blanco C, Han B, Jones CM, Johnson K, Compton WM. Prevalence and correlates of benzodiazepine use, misuse, and use disorders among adults in the United States. J Clin Psychiatry. 2018;79(6)
4. Drugabuse.gov. Overdose Death Rates. [online]. 2019. Available at: https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates. Accessed 9 May 2019.
5. McHugh RK, Votaw VR, Bogunovic O, Karakula SL, Griffin ML, Weiss RD. Anxiety sensitivity and nonmedical benzodiazepine use among adults with opioid use disorder. Addict Behav. 2017;65:283–8.
6. Kan CC, Hilberink SR, Breteler MH. Determination of the main risk factors for benzodiazepine dependence using a multivariate and multidimensional approach. Compr Psychiatry. 2004;45(2):88–94.
7. Griffin CE, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system–mediated effects. Ochsner J. 2013;13(2):214–23.
8. Msp.scdhhs.gov. [online]. 2019. Available at: https://msp.scdhhs.gov/tipsc/sites/default/files/tipSC%20Mar%202018%20benzoequivtable%2042018.pdf. Accessed 10 May 2019.
9. Vhpharmsci.com. Comparison of Benzodiazepines. [online]. 2019. Available at: http://www.vhpharmsci.com/vhformulary/tools/benzodiazepines-comparison.htm. Accessed 10 May 2019.
10. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). Arlington, VA: American Psychiatric Publishing; 2013 May 22.
11. Gaudreault P, Guay J, Thivierge RL, Verdy I. Benzodiazepine poisoning. Drug Saf. 1991;6(4):247–65.
12. Nasky KM, Cowan GL, Knittel DR. False-positive urine screening for benzodiazepines: an association with sertraline?: a two-year retrospective chart analysis. Psychiatry (Edgmont). 2009;6(7):36.
13. Weinbroum AA, Flaishon R, Sorkine P, Szold O, Rudick V. A risk-benefit assessment of flumazenil in the management of benzodiazepine overdose. Drug Saf. 1997;17(3):181–96.
14. Schöpf J. Withdrawal phenomena after long-term administration of benzodiazepines a review of recent investigations. Pharmacopsychiatry. 1983;16(01):1–8.
15. Denis C, Fatseas M, Lavie E, Auriacombe M. Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. Cochrane Database Syst Rev. 2006;3
16. Sadock BJ, Sadock VA. Kaplan and Sadock's synopsis of psychiatry: behavioral sciences/clinical psychiatry: Philadelphia, PA: Lippincott Williams & Wilkins; 2015.
17. Sivilotti ML. Flumazenil, naloxone and the 'coma cocktail'. Br J Clin Pharmacol. 2016;81(3):428–36.
18. Gunja N. The clinical and forensic toxicology of Z-drugs. J Med Toxicol. 2013;9(2):155–62.
19. Salvà P, Costa J. Clinical pharmacokinetics and pharmacodynamics of zolpidem. Clin Pharmacokinet. 1995;29(3):142–53.
20. Brielmaier BD. Eszopiclone (Lunesta): a new nonbenzodiazepine hypnotic agent. In Baylor University Medical Center Proceedings 2006 Jan 1 (vol. 19, no. 1, pp. 54–59). Taylor & Francis.
21. Dooley M, Plosker GL. Zaleplon. Drugs. 2000;60(2):413–45.
22. Sankar R. GABA(A) receptor physiology and its relationship to the mechanism of action of the 1,5-benzodiazepine clobazam. CNS Drugs. 2012;26(3):229–44. https://doi.org/10.2165/11599020.
23. Twyman RE, Rogers CJ, Macdonald RL. Differential regulation of γ-aminobutyric acid receptor channels by diazepam and phenobarbital. Ann Neurol. 1989;25(3):213–20.

Cannabinoids

10

Joao P. De Aquino and Bachaar Arnaout

High-Yield Review Points

- The psychoactive components and activity of cannabis and cannabinoid products vary widely, and most safety data are derived from studies conducted with products less potent than ones currently available.
- Cannabinoids have dose-dependent, often biphasic, and time-dependent effects. While medical use of cannabinoids may benefit a select group of patients, systematic scientific evidence supporting most claims remains limited.
- Because of tolerance, patients may gradually require more cannabinoids to achieve a desired effect, and abrupt discontinuation may precipitate a withdrawal syndrome.
- Cannabinoids may impair cognition, and the effect can be potentiated when combined with other psychoactive substances including opioids, benzodiazepines, and alcohol, or when used by those with neurocognitive disorders.
- Individuals with major psychiatric disorders and adolescents may be more prone to developing adverse effects of cannabinoids.
- New onset or worsening of anxiety, mood disturbance, cognitive impairment, or psychosis should prompt clinical evaluation of whether cannabinoids are a contributing factor.

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Epidemiology and Recent Trends in Cannabinoid Use

Cannabis is one of the most widely used substances in the United States. According to the 2016 National Survey on Drug Use and Health (NSDUH), 127.5 million individuals – approximately 45% of Americans aged 12 years or older – used cannabis in their lifetime [1]. Approximately 41 million individuals used cannabis in the past year, and three million used for the first time, which amounts to approximately 8300 new users each day [1]. From 1992 until 2012, the proportion of Americans regularly using cannabis increased by roughly 60%. Several factors may account for this, such as increased perception of cannabis as "benign" and higher social acceptability, especially among adolescents. Of the three million individuals using cannabis for the first time in 2016, most were under the age of 18. Consistent with this, since the Monitoring the Future (MTF) survey of 12th graders began in 1975, the perceived risk of cannabis use has declined, and the prevalence has increased, with nearly 8% of all youth aged 12 to 17 currently smoking cannabis [2].

Medical and Recreational Cannabinoid Use Policy In recent years, there have been several changes to legislation surrounding the use of cannabinoids, with several US states and other jurisdictions in Europe, and South and Central America moving toward legalization.

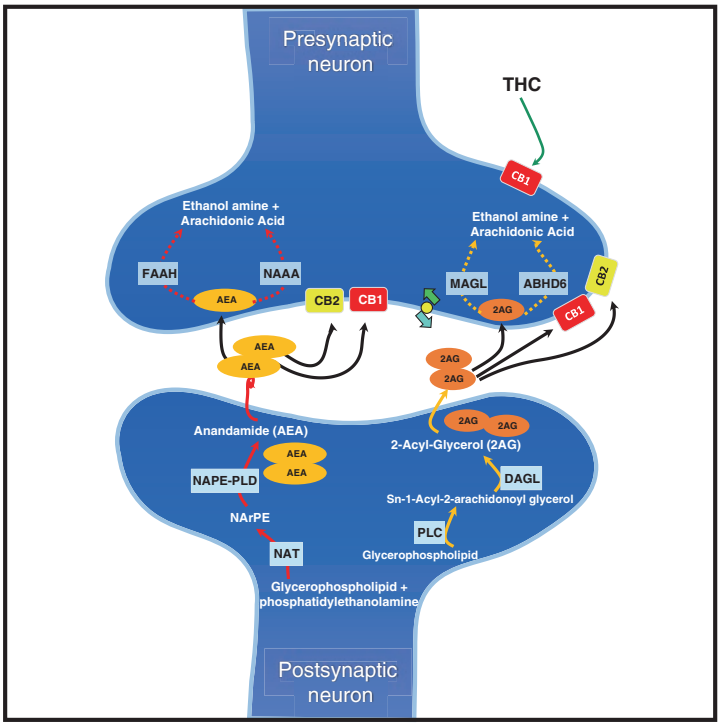
In the United States, medical cannabis programs were originally promoted as compassionate care initiatives for terminally ill patients. They were created to guarantee the rights of patients using cannabis to treat nausea, cachexia, or spasticity. Between 1979 and 1991, five states – Virginia (1979), New Hampshire (1981), Connecticut (1981), Wisconsin (1988), and Louisiana (1991) – approved medical cannabis legislation. Since 1996, as of the beginning of 2019, starting with California, 33 states and the District of Columbia have authorized the possession of cannabis for medical purposes, or have created state agencies to license the production and dispensation of medical cannabis**.** In these states, physicians can recommend medicinal use of cannabis to patients with qualifying conditions; though, since it is still considered a Schedule I substance under federal law, they do not have the authority to *prescribe* it. Notably, there is significant inconsistency between states regarding which are the qualifying conditions, and, more importantly, there is great discrepancy between what is allowed under state law and the scientific evidence base – which thus far supports cannabinoid-based therapeutics for nausea and vomiting, in addition to specific types of pain, such as neuropathic pain and spasticity related to multiple sclerosis. In many states, individuals may receive recommendations for cannabis from physicians whom they have seen for a single visit and with whom they do not regularly follow-up for standard care.

At the time of writing, Canada, 10 US states, and the District of Columbia have also allowed cannabis for recreational use by adults over 21 years old**.** Given rapid societal changes, elucidating what is known about the impact of cannabinoid use on mental health takes on urgent public health importance.

Pharmacology

Overview of the Endocannabinoid System

The endocannabinoid (eCB) system is one of the most widespread systems in the central nervous system (Fig. 10.1). It consists of receptors, endogenous transmitters or eCBs, and enzymes that synthesize and degrade eCBs, including fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). The two main receptors



CB1 Cannabinoid receptors located mainly centrally

AEA Anandamide

NAT N-acyltransferase

NAPE-PLD N-acylphosphatidylethanolamine-selective phospholipase D

FAAH Fatty acid amide hydrolase

NAAA N-Acylethanolamine-Hydrolyzing Acid AmidaseSolid

arrows: synthetic pathway

CB2 Cannabinoid receptors located mainly peripherally

2AG 2-arachidonoylglycerol

DAGL Diacylglycerol lipase

PLC Phospholipase C

MAGL Monoacylglycerol lipase

ABHD6 2-arachidonoylglycerol hydrolase

Dotted arrows: degradation pathway

Endocannabinoid cell membrane transporter?

Fig. 10.1 The endocannabinoid system. *ABHD6* 2-arachidonoylglycerol hydrolase; *AEA* anandamide; *2AG* 2- arachidonoylglycerol; *CB1* cannabinoid receptors located mainly centrally; *CB2* cannabinoid receptors located mainly peripherally; *DAGL* diacylglycerol lipase; *FAAH* fatty acid amide hydrolase; *MAGL* monoacylglycerol lipase; *NAAAN* acylethanolamine-hydrolyzing acid amidase; *NAPE-PLD* N-acylphosphatidylethanolamine-selective phospholipase D; *NAT* N-acyltransferase; *PLC* phospholipase C; *Solid arrows* synthetic pathway; *dotted arrows* degradation pathway

are the G-protein-coupled receptors cannabinoid-1 receptor (CB1R) and cannabinoid-2 receptor (CB2R). In addition, some cannabinoids engage transient receptor potential (TRP) channels and peroxisome proliferator-activated receptors (PPARs). The two most well-studied eCBs include the lipid ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG). CB1Rs are densely expressed in the brain and critical in mediating the psychoactive effects of cannabis, as they are the targets of tetrahydrocannabinol (THC), a partial agonist at these receptors. CB2Rs, in contrast, are mostly expressed peripherally (immune, gastrointestinal, and peripheral nervous systems).

Plant-Based Cannabinoids

Cannabis is a complex and highly variable mixture of approximately 400 or more chemical compounds, including plant-based cannabinoids (or phytocannabinoids), terpenoids, and flavonoids that produce individual and interactive effects. Delta-9-tetrahydrocannabinol (THC) is the principal psychoactive constituent of cannabis. Some of the other 70 currently known phytocannabinoids also have individual effects. For example, cannabidiol (CBD) may have anxiolytic and antipsychotic-like effects that offset THC-induced anxiety and psychotomimetic effects. Preclinical studies suggest the individual effects of phytocannabinoids are multi-phasic and dose-dependent, which is exemplified by the anxiolytic effects of THC at lower doses, and anxiogenic effects at higher doses. An interesting aspect of cannabinoids is that they exhibit a phenomenon known as the "entourage effect" – which means that their activity can be enhanced by structurally related – but otherwise biologically inactive – constituents [3].

Synthetic Cannabinoids

Synthetic cannabinoids (SC) originated from basic research on cannabinoid agonists. They are full CB1R receptor agonists, and up to 800 times more potent than plant-based cannabinoids. The various products sold as "spice" or "K2" often contain diverse compounds. The effects of SC products are generally more pronounced than those of cannabis, including higher levels of anxiety, psychotomimetic effects, hypertension, and tachycardia. Also, because some of the products contain cathinones (or "bath salts") combined with SCs, there have been cases of life-threatening or fatal effects, including seizures, toxic hepatitis, cardiac ischemia, and stroke. The withdrawal symptoms are similar in time course to those of cannabis; however, they also tend to be more pronounced and to involve somatic symptoms such as nausea and vomiting.

SC use is more likely among individuals who use cannabis, users of other synthetic drugs, and individuals who may try to avoid detection by commonly administered drug urine screens that typically only screen for THC (e.g., those on probation, in the military, or in workplaces that utilize drug testing).

Clinical Significance and What Psychiatrists Should Know About Cannabinoids

Available Cannabis Products

Varieties of cannabis, cannabis-based products, and synthetic cannabinoids (SC) differ widely in their cannabinoid proportion and content (Table 10.1). It is increasingly recognized that THC content (potency) of cannabis in the United States has steadily increased over the past decades, from 4% in 1995 to 12% in 2014. Some potent strains of cannabis have a THC content of approximately 30%, and other cannabis-based products have a THC content of over 80% [4]. In comparison, the cannabis made available by the National Institute of Drug Abuse (NIDA) for

Table 10.1 Currently available cannabinoid products

Cannabinoid product	Description	Method of use
Smoked products	Dried cannabis leaves and flowers ("marijuana")	Smoked in hand-rolled cigarettes ("joints", "blunts"), pipes with filtration systems created to reduce the harshness and temperature of the smoke ("bong", "hookah"), or vaporizers
Hashish	Concentrated trichomes with a higher THC concentration than other parts of the plant	Smoked or mixed with food.
Kief	Powder extracted from THC-rich trichomes (resin glands)	Smoked or compressed into hashish "cakes"
Hash oil	A mixture of essential oils and resins extracted from the cannabis plants using solvents, such as ethanol or butane	The solvent is evaporated, leaving a THC-rich oil that can be smoked, vaporized, or mixed with food
Edibles	Food products infused with cannabis	Directly added cannabis, or cannabis butter or oil. Can be alcoholic beverages
Tincture	Cannabinoids extracted using alcohol	Liquid form, absorbed through the mucous membranes (oral mucosa or sublingually)
Topicals	Oils infused with cannabis	Salve or cream applied topically
Skunk	*Cannabis* strains that are strong-smelling and THC-rich	Smoked
Shatter	A cannabis concentrate with a transparent, amber appearance that looks glassy when cold, and like thick honey when warm	"Dabbing" (special pipe) or vaporizing
Wax	Opaque cannabis concentrate with a buttery appearance. Different wax consistencies are created using varying oil textures and different moisture and heat levels.	"Dabbing" (special pipe) or vaporizing

THC Delta-9-tetrahydrocannabinol

research purposes has less than 4% THC, and so, the limited studies with cannabis do not reflect products being used. The THC/CBD ratio has also increased, such that many popular forms of cannabis have low CBD and high THC content.

Associated Effects

Acute Intoxication

The onset of cannabinoid effects depends on the route of administration, with effects emerging within minutes after inhalation, but taking hours (60–90 minutes) following oral consumption [5]. The duration of effects is highly variable but usually lasts for 2 (inhaled) to 4 hours (oral). The acute effects of cannabinoids are likely to be more pronounced with higher doses, higher THC/CBD ratio, and with full agonists, such as SCs. It is not fully understood why some healthy individuals are more vulnerable than others to the acute effects of cannabinoids. Individuals who use cannabinoids regularly may show blunted responses due to tolerance.

Behavioral Effects

Mood/Anxiety Cannabis may produce acute transient effects on mood. The "high" produced by cannabis includes a combination of effects reported as relaxation, euphoria, relaxed inhibitions, and an overall sense of well-being. Although cannabis is generally anxiolytic, especially at lower doses, the higher concentration of THC found in cannabis in recent years has probably led to an increase in reports of panic-like effects. THC has been reported to increase anxiety when administered alone, especially at high doses, and under conditions of stress, while co-administration with CBD can counter THC-induced anxiety.

There are observational reports of elevated mood and reduced depressive symptoms following short-term consumption of cannabis, which are blocked by CB1R antagonists. However, it is challenging to differentiate this from the euphoria induced by cannabis intoxication. Further, the administration of a CB1R inverse agonist (rimonabant) to healthy individuals increased anxiety, depression, and suicidal ideation. The evidence for the antidepressant effects of herbal cannabis remains contradictory, as brief dysphoric reactions are also well-recognized consequences of acute cannabis use, especially to those who are cannabis naïve.

Psychosis Cannabis intoxication is associated with transient psychosis-like effects that include depersonalization, derealization, ideas of reference, grandiose and paranoid delusions, flight of ideas, disorganized thinking, and auditory and visual hallucinations. These effects have been increasingly reported with high-THC strains of cannabis and SCs, and individuals with psychosis liability or a family history of psychosis are more prone to experiencing psychotomimetic effects.

Cognitive Effects Cannabis can acutely impair various cognitive domains. Daily heavy users of cannabis may have blunted responses to the cognitive deficits induced by cannabis, and in these populations abstinence from cannabis may in fact be associated with cognitive impairment [6]. The acute effects of cannabis on cognition may depend on the THC/CBD ratio, with higher concentrations of CBD reducing cognitive deficits.

Attention Deficits in selective, focused, and divided attention tasks can be induced by cannabis. In addition, allocation of attention and signal detection have been demonstrated after acute administration of both cannabis and THC to healthy individuals. Impaired performance on a divided attention task following administration of THC was shown in only occasional, but not heavy, users, indicating tolerance.

Memory Cannabis may affect spatial working memory, procedural memory, verbal learning and recall, and associative learning [6]. Deficits in verbal learning and memory are recognized as the most robust impairments associated with acute cannabis use. THC was shown to interfere with encoding, but not retrieval of verbal memory, suggesting that learning information prior to using cannabinoids is not likely to disrupt recall of that information. Whether THC impairs encoding of nonverbal information and memory consolidation remains to be elucidated [7]. The activation of CB1Rs, especially in the hippocampus, which contains a high density of these receptors, may interfere with short-term memory, and may impair memory consolidation.

Inhibitory Control Impairment of inhibitory control has been shown following acute cannabis intoxication, and THC and CBD may have opposite effects on response inhibition following "Go/NoGo" tasks. It has been proposed that the eCB system may modulate dopaminergic tone in the prefrontal cortex and nucleus accumbens, contributing to incentive salience to specific stimuli and impulsivity, and that THC disrupts these physiological mechanisms underlying inhibitory and decision-making processes [8].

Motoric Effects and Relevance for Driving Ability

Consistent with the known distribution of CB1Rs in areas involved in cognitive and motor processes (i.e., brain cortex, basal ganglia, and cerebellum), driving simulation studies collectively suggest that cannabinoids produce acute impairments in driving ability, exemplified by an increase in lateral position errors and lane deviation, steering instability, braking distance, and collisions. Impairment can be further pronounced while under the influence of other substances such as alcohol or prescribed drugs (i.e., benzodiazepines or opioids).

Effects of Chronic Use

Cognitive Effects

The chronic cognitive effects of cannabinoids are more complex and controversial than their acute effects, appearing to be related to the dose of exposure and age of onset of use [7]. The evidence is stronger for impairments in verbal learning and memory, as well as working memory and attention, with mixed evidence for effects on decision-making. Whether these impairments are permanent is not fully understood.

In one of the largest and longest prospective studies controlling for premorbid function, Meier et al. reported that cannabis use before the age of 18 resulted in greater decline in intelligence by age 38, persisting even after cessation or reduction of use in the past year. A recent meta-analysis, conversely, found that only small magnitude effects are apparent in the first few weeks of abstinence (of the order of $d = 0.25$ to 0.35), and these become non-significant with extended abstinence (to around $d = 0.15$) [9].

Cannabis Use Disorder

Cannabis use disorder (CUD) is the most prevalent substance use disorder (SUD) in the general US population after alcohol and nicotine use disorders. Approximately 1 in 10 individuals who use cannabis progress to compulsive use at the CUD level. In the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III), the lifetime prevalence of CUD was 6.3%. The lifetime rates of CUD in those who begin use in adolescence have been reported to be close to 17% [10]. Importantly, participants in the NESARC-III with CUD experienced considerable disability across a variety of domains. Their level of disability correlated with the frequency of cannabis use and was greater than the corresponding levels of disability associated with alcohol use disorder [11].

It is unclear whether medical cannabis is associated with lower or higher levels of CUD, although some evidence suggests the latter, as states where medical cannabis is legal had higher rates of CUD diagnoses among veterans in 2002, 2008, and 2009 [12].

Some evidence suggests that regular cannabinoid use might be implicated in the development of SUDs other than CUD (i.e., the "gateway hypothesis" of cannabis). Approximately 1 in 10 cannabis users develop a SUD other than CUD, and this number is higher among adolescents [12]. In a large nationally representative sample, cannabis use was prospectively associated with increased prevalence and incidence of alcohol and other SUDs, after adjusting for several covariates that predicted cannabis use. It has also been proposed that the neurocircuitry involved in mediating the effects of cannabis overlaps with that involved in other substances. It is not fully clear whether overlap may contribute cross-sensitization to other substance use, rather than a common underlying vulnerability across distinct substances [12].

Cannabis Withdrawal Syndrome

Recognized in DSM-5 as a distinct entity, cannabis withdrawal syndrome (CWS) is characterized by anger, aggression, appetite change, weight loss, irritability, anxiety, restlessness, sleep disturbance, cannabis craving, and physical discomfort. Other, less common symptoms include chills, depressed mood, stomach pain, and diaphoresis. Most symptoms appear within one day of abstinence, peak within 2–3 days, and resolve within 1–3 weeks. However, some studies suggest that withdrawal symptoms may persist longer than 4 weeks, especially sleep disturbances.

Adolescent Psychiatric Disorders

In general, the adolescent brain differs from the adult brain in that the adolescent brain is more susceptible to external influences. As a result, adolescents are more likely to develop psychiatric consequences of prolonged cannabis use. The mesolimbic dopaminergic system and the hypothalamic pituitary-adrenal-axis (HPA) both develop earlier than the prefrontal cortex (PFC), and such differences result largely from the incomplete structural and functional maturity of the PFC. The eCB system regulates developmental processes through the brain, including pyramidal cell specification, interneuron migration and morphogenesis, neuronal connectivity, and synaptic plasticity, which all contribute to the maturation of the PFC. The influence of exogenous cannabinoids may interfere with these processes, increasing the risk of psychiatric disorders.

Psychotic Disorders Transient, cannabis-induced psychosis is often clinically indistinguishable from a primary psychotic disorder, and can outlast the period of acute intoxication and persist for as long as 30 days. Although most people who consume cannabis do not experience psychosis, the cannabis-psychosis link may occur in those with predisposing genetic and environmental factors. As with other negative effects of cannabis, the risk of psychosis appears to be heightened by heavy and early use.

Cannabis use has also been shown to exacerbate the course of illness in individuals with established psychotic disorders [13]. With the rising potency of cannabis strains and more frequent use, there is some evidence that the age of onset of first-episode psychosis is decreasing. Consistent with this, SC users are generally more frequently diagnosed with psychotic disorders.

Anxiety Disorders Long-term cannabis use can exacerbate anxiety, cause panic attacks, and exacerbate the neuroendocrine response to stress. While individuals with anxiety disorders report a high incidence of cannabis use, whether cannabis is used to try to decrease anxiety, or whether it contributes to anxiety disorders may be difficult to discern clinically. Cannabis use has also been associated with social anxiety disorder.

Mood Disorders Cannabis use is associated with a worse clinical course of mood disorders, including more frequent hospitalizations, more frequent and longer manic episodes, and greater prevalence of psychotic symptoms in individuals with bipolar disorder [12]. There is also preliminary evidence of cannabis use conferring a higher risk for bipolar and depressive disorders. Conversely, both unipolar and bipolar mood disorders appear to increase rates of cannabis use and CUD in prospective studies.

Attention-Deficit/Hyperactivity Disorder (ADHD) Preliminary data indicate that ADHD is a risk factor for developing cannabis misuse in adulthood. However, the impact of cannabis use on the course of ADHD is not fully clear. Some evidence indicates that specific phenotypes of ADHD may be more closely associated with distinct patterns of cannabis use (i.e., the inattention type is associated with more severe cannabis use, and the hyperactivity-impulsivity phenotype is associated with earlier onset of cannabis use). Though data are sparse, it appears that chronic, and especially early cannabis use, is associated with negative outcomes in ADHD, including further attention deficits, and refractoriness of hyperactivity and impulsivity to pharmacological treatment [12].

Sleep Disorders The relationship between cannabis use and sleep is complex, in that time-dependent effects, as well as intoxication and withdrawal must be considered. Overall, cannabis use is associated with reduced rapid eye movement (REM) sleep, shortening of sleep-onset latency, and increased stage 4 sleep. Sedation after cannabis exposure may continue into the following day [14]. Further, insomnia and vivid dreams are common during CWS [15], especially among heavy users. Preliminary evidence also indicates childhood-onset sleep disorders may predict cannabis and alcohol use in adolescence and early adulthood [16].

Posttraumatic Stress Disorder Individuals with posttraumatic stress disorder (PTSD) have higher rates of cannabis use – as well as SUDs in general – than the general population. Thus far, there is no evidence, however, that cannabis use is a risk factor for the development of PTSD. Although cannabis is increasingly being offered as a treatment for PTSD, systematic reviews indicate that the evidence examining its benefits and harms in patients with this disorder is still conflicting and incomplete.

Treatment of Cannabis Use Disorder

Assessment of Cannabis Use

Individuals who use cannabis and seek treatment typically have used nearly every day for more than 10 years, and have tried to quit approximately 7 times. A small minority presents to addiction specialty treatment with specific concerns about cannabis misuse. More frequently, individuals present to general psychiatric treatment

or primary care settings, with symptoms of depression, anxiety, fatigue, impaired concentration, irritability, or relationship stress. Individuals with high-intensity use may present to emergency departments with acute anxiety, psychotomimetic effects, or altered mental status. Adolescents present with declining school performance, whereas adults may experience impaired performance at work.

Several screening tools may assist the clinician in assessing cannabis use, including the Cannabis Use Problems Identification Test (CUPIT) [16], the Severity of Dependence Scale (SDS), and the Cannabis Problems Questionnaire. Terminology relating to cannabis is highly regional, as are the names of distinct cannabis strains. Clinicians should have some working knowledge about the ways cannabis is consumed and common cannabis products and forms to adequately assess use.

Pharmacological Interventions

Currently, there are no FDA-approved medications for treating CUD, although there is increased interest in drug development, given the recognition of a cannabis withdrawal syndrome, and greater understanding of the physical and societal burden of cannabis misuse.

A large 12-week RCT did not find that dronabinol (20 mg twice daily) improved abstinence during a two-week maintenance phase (dronabinol 17.7% vs. placebo 15.6%), though treatment retention and relief of withdrawal symptoms were better in the dronabinol group. Similarly, a two-site RCT investigating the effectiveness of nabiximol, a 1:1 ratio of THC and CBD in a spray formulation, for the treatment of CUD found that after 28 days the treatment and placebo groups showed no difference in self-reported cannabis use.

Antidepressants, buspirone, divalproex sodium, and lithium do not appear to be particularly useful for treating CUD, and little research informs a rational pharmacological approach to co-occurring psychiatric disorders. There are preliminary data for gabapentin, cannabinoid degradative enzyme inhibitors (FAAH inhibitors) [17], and glutamate modulators (N-acetylcysteine) for reducing cannabis use. N-acetylcysteine was found to reduce cannabis use in non-treatment seeking adolescents [16], but not adults. Lofexidine, recently FDA-approved to treat opioid withdrawal, has been shown to decrease symptoms of cannabis withdrawal.

Despite the limitations of the current literature, findings from basic science and human laboratory studies provide reasons for optimism that further clinical studies will lead to clinically meaningful pharmacotherapeutic interventions CUD and cannabis withdrawal.

Psychosocial Interventions

Research on psychosocial treatments for CUD demonstrates moderately successful strategies. These interventions enhance skills than can be used to prevent return to use or decrease use [such as cognitive behavioral therapy (CBT)], foster internal

motivation [such as motivational enhancement therapy (MET)], or provide external incentives for interest in treatment plans to stop or decrease use [such as contingency management (CM)]. A meta-analysis of psychosocial intervention studies (CBT, CM, and MET) indicates that cannabis users who receive these treatments fare better than 66% of those in the control conditions for outcomes such as frequency and severity of use, and psychosocial functioning.

In recent times, there has been interest in software-based interventions, aiming to increase dissemination and reduce the cost of evidence-based treatments outside of traditional clinical settings. Various placebo-controlled studies indicate web-based interventions hold promise for treatment of CUD.

Medical Use of Cannabinoids: Indications, Formulations, and Adverse Effects

Qualifying indications for medical cannabis use vary by state; however, evidence for most indications remains scant or preliminary. The most consistent evidence pertains to neuropathic pain, spasticity related to multiple sclerosis, and nausea and vomiting. Several pharmaceutical formulations of cannabinoids are available or under development in the United States. Dronabinol and nabilone are FDA-approved for the treatment of chemotherapy-induced nausea and vomiting. Dronabinol is also approved for the treatment of AIDS-associated anorexia. Nabiximols, administered in a spray form and containing THC and CBD in a 1:1 ratio, has been approved in Canada to treat cancer-related pain and multiple sclerosis-related spasticity, and a US phase 3 trial is planned to test this drug for the latter indication. The FDA has also recently approved CBD for a rare form of seizure disorder in the pediatric population.

Interactions of Cannabinoids with Other Drugs

Pharmaceuticals that may interact with cannabis in a clinically significant manner include antiplatelet and anticoagulant agents, chemotherapy agents, antivirals, barbiturates, and some antibiotics. Cannabis can also induce mood changes when used with antidepressants, and can have synergistic effects with alcohol and other central nervous system depressants (Table 10.2).

Genetic Factors

Genetic variation accounts for part of the variance of the risk of initiation and maintenance of cannabis use. A meta-analysis of twin studies reported heritability estimates of approximately 40%, with estimates ranging from 17–70% for lifetime use and 33–76% for CUD. A recent meta-analysis of genome-wide association studies, however, found that no genetic variant reached genome-wide significance, and that only about 6% of cannabis use initiation was due to common genetic variants.

Table 10.2 Cannabis-pharmaceutical interactions

Mechanism	Drugs
Antiestrogenic effect	Contraceptive medications Hormone replacement therapy
Competition with metabolism, leading to increased drug levels	Barbiturates (phenobarbital, pentobarbital, secobarbital)
Inhibition of platelet aggregation	Nonsteroidal anti-inflammatory drugs Anticoagulants (warfarin) Antiplatelet agents (clopidogrel)
Induction of cytochrome P450 2E1, leading to decreased levels of substrate drugs	Acetaminophen, ethanol, theophylline, anesthetics (enflurane, halothane, isoflurane)
Inhibition of cytochrome P450 3A4, leading to increased levels of substrate drugs	Lovastatin, cyclosporine, diltiazem, indinavir, triazolam, clarithromycin
Inhibition of P-glycoproteins, leading to increased levels of substrate drugs	Chemotherapy agents (etoposide, paclitaxel, vinblastine, vincristine, vindesine) Antifungals (ketoconazole, itraconazole) Protease inhibitors (amprenavir, nelfinavir, saquinavir, indinavir) Histamine H2 antagonists (cimetidine, ranitidine) Calcium channel blockers (diltiazem, verapamil) Corticosteroids Others (quinidine, cyclosporine, loperamide, quinidine, erythromycin, fexofenadine)
Additive/synergistic effects	Ethanol Other central nervous system depressants

Adapted from: Compton [18]

Review Questions

1. A 21-year-old man started using cannabis at age 15 and found himself escalating his daily use at age 17 to achieve the same desired effect. He feels "jittery" and "depressed," and cannot sleep when he stops using cannabis. He was an above-average student in junior high school, but his performance and grades subsequently fell and he often felt unmotivated. Despite wanting to pursue a college education, he missed several application deadlines. He took a job at a local coffee shop, because the short work shifts allowed more time to use cannabis alone at home. Which of the following diagnoses best describes this presentation?
   A. Cannabis hyperemesis syndrome
   B. Cannabis withdrawal syndrome
   C. Chronic cannabis syndrome
   D. Cannabis use disorder

   Answer D.

Explanation: This individual has symptoms of tolerance, withdrawal, difficulty with major role obligations in school and work, which are diagnostic criteria for cannabis use disorder. He does not present with the persistent nausea or vomiting of hyperemesis syndrome, or with the irritability after cannabis cessation of withdrawal. Chronic cannabis syndrome is not a DSM-5 diagnosis.

2. A 20-year-old woman has smoked hashish daily for the past 12 months. She was stopped by the police for driving while intoxicated and held in custody over the weekend until her court hearing on Monday. While unable to use hashish, which of the following sets of symptoms is she most likely to experience?
   A. Muscle twitches, lacrimation, rhinorrhea, and diarrhea
   B. Nausea, headache, irritability, vomiting, and insomnia
   C. Hallucinations, tachycardia, and hypertension
   D. Slurred speech, vomiting, ataxia, and hypotension

   Answer: B.

   Explanation: This person is likely to experience cannabis withdrawal syndrome. Muscle twitches, lacrimation, rhinorrhea, and diarrhea tend to occur with opioid withdrawal. Hallucinations, tachycardia, and hypertension are common with severe alcohol withdrawal. Slurred speech, ataxia, vomiting, and hypotension occur during opioid intoxication.

3. A 22-year-old man develops paranoid delusions and dissociative symptoms over seven months, until he is hospitalized for an episode of behavioral dysregulation. He reports smoking five joints of cannabis daily since the age of 13. He is diagnosed with unspecified psychotic disorder and started on an antipsychotic medication. Which of the following best describes the current scientific consensus regarding the relationship between cannabis use and psychotic disorders?
   A. Schizophrenia is caused by early cannabis use
   B. Prodromal psychotic symptoms are temporarily relieved by cannabis
   C. The development of a psychotic disorder is independent of cannabis use
   D. Though the relationship between psychosis and cannabis use is complex, cannabis does appear to be a risk factor for the development of psychosis

   Answer: D.

   Explanation: Cannabis use is a risk factor for psychosis; however, it is neither sufficient to cause it, as answer A suggests it, nor necessary. In this clinical scenario, it is likely that prolonged and heavy cannabis use contributed to the onset of the psychotic disorder. There is no evidence to suggest prodromal symptoms of psychosis are relieved by cannabis.

References

1. Ahrnsbrak R, Bose J, Hedden S, Lipari R, Park-Lee E. Key substance use and mental health indicators in the United States: results from the 2016 National Survey on Drug Use and Health. Rockville: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2017.

2. Johnston LD, O'Malley PM, Miech RA, Bachman JG, Schulenberg JE. Monitoring the future National Survey Results on Drug Use, 1975–2016: overview, key findings on adolescent drug use. Institute for Social Research; 2017.
3. Azofeifa A. National estimates of marijuana use and related indicators—National Survey on Drug Use and Health, United States, 2002–2014. MMWR Surveill Summ. 2016;65:1.
4. Rey AA, Purrio M, Viveros MP, Lutz B. Biphasic effects of cannabinoids in anxiety responses: CB1 and GABA(B) receptors in the balance of GABAergic and glutamatergic neurotransmission. Neuropsychopharmacology. 2012;37(12):2624–34.
5. ElSohly M, Gul W. Constituents of Cannabis sativa. In: Handbook of Cannabis, vol. 3; 2014. p. 1093.
6. ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC. Changes in Cannabis potency over the last 2 decades (1995–2014): analysis of current data in the United States. Biol Psychiatry. 2016;79:613.
7. Ranganathan M, D'souza DC. The acute effects of cannabinoids on memory in humans: a review. Psychopharmacology. 2006;188(4):425–44.
8. Ramaekers JG, Kauert G, Theunissen EL, Toennes SW, Moeller MR. Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. J Psychopharmacol. 2009;23(3):266–77.
9. Borgwardt SJ, Allen P, Bhattacharyya S, Fusar-Poli P, Crippa JA, Seal ML, et al. Neural basis of Δ-9-tetrahydrocannabinol and cannabidiol: effects during response inhibition. Biol Psychiatry. 2008;64(11):966–73.
10. Dubois S, Mullen N, Weaver B, Bedard M. The combined effects of alcohol and cannabis on driving: impact on crash risk. Forensic Sci Int. 2015;248:94–100.
11. Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci U S A. 2012;109(40):E2657–64.
12. Blanco C, Hasin DS, Wall MM, Flórez-Salamanca L, Hoertel N, Wang S, et al. Cannabis use and risk of psychiatric disorders: prospective evidence from a US national longitudinal study. JAMA Psychiat. 2016;73(4):388–95.
13. Bonn-Miller MO, Harris AH, Trafton JA. Prevalence of cannabis use disorder diagnoses among veterans in 2002, 2008, and 2009. Psychol Serv. 2012;9(4):404–16.
14. Sibley MH, Pelham WE Jr, Molina BS, Coxe S, Kipp H, Gnagy EM, et al. The role of early childhood ADHD and subsequent CD in the initiation and escalation of adolescent cigarette, alcohol, and marijuana use. J Abnorm Psychol. 2014;123(2):362.
15. Bidwell L, Henry E, Willcutt E, Kinnear M, Ito T. Childhood and current ADHD symptom dimensions are associated with more severe cannabis outcomes in college students. Drug Alcohol Depend. 2014;135:88–94.
16. Schierenbeck T, Riemann D, Berger M, Hornyak M. Effect of illicit recreational drugs upon sleep: cocaine, ecstasy and marijuana. Sleep Med Rev. 2008;12(5):381–9.
17. D'Souza DC, Cortes-Briones J, Creatura G, Bluez G, Thurnauer H, Deaso E, et al. Efficacy and safety of a fatty acid amide hydrolase inhibitor (PF-04457845) in the treatment of cannabis withdrawal and dependence in men: a double-blind, placebo-controlled, parallel group, phase 2a single-site randomised controlled trial. Lancet Psychiatry. 2019;6(1):35–45.
18. Compton MT, editor. Marijuana and mental health: American Psychiatric Publishing; 2016.

Opioids

11

Marina Tsoy-Podosenin and Anil Thomas

High-Yield Review Points

- The diagnosis of OUD is based on the presence of two or more criteria related to loss of control, risky use, social problems, and physical dependence within the same 12-month period. Detailed drug and medical history, presence of characteristic signs of drug use on physical evaluation, and toxicology results play an important role in diagnostics of OUD.
- Opioid intoxication may result in overdose and death. Risk of overdose increases if opioid use is combined with other sedatives, e.g., alcohol, benzodiazepines, barbiturates, etc., as well as in patients who recently completed detoxification or after a period of prolonged abstinence (e.g., former inmates) due to reduced tolerance. Naloxone hydrochloride for intranasal, intravenous, intramuscular, and subcutaneous use effectively reverses opioid overdose.
- Opioid withdrawal, although generally not life-threatening, and opioid craving are often the main drivers in continuation of opioid use. Medical management of opioid withdrawal involves use of full (methadone) or partial opioid agonists (buprenorphine), alpha-2 adrenergic agonists and medications providing symptomatic relief.
- Opioid maintenance treatment decreases illicit opioid use and improves function and includes a combination of pharmacological agents (opioid agonists or antagonists) with counseling and psychosocial support. Specific indications, availability of pharmacological agents, and patient's motivation and health condition should be taken into consideration.

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Introduction

Opioid use disorder is a chronic, relapsing disease, which has significant economic, personal, and public health consequences. The term *opiate* refers to a subset of the opioids, the compounds directly derived from or synthesized from the natural product thebaine and its derivatives isolated from the poppy plant, with or without further synthetic modifications (e.g., codeine, morphine and heroin). The term *opioid* is used to refer to the entire class of compounds that bind to one or more types of opioid receptors, including endogenous peptides, natural alkaloids, and synthetic and semi-synthetic chemicals. The difference between these terms has implications for the standard urine drug screen that typically only detects *opiates*. *Narcotics* are non-medical and/or illegal drugs that dull the senses, alter perceptions, or affect mood or behavior. *Controlled substances* are listed in the five schedules made after the Harrison Narcotic Act of 1914 and the Controlled Substances Act from 1970 that includes Schedule 1 drugs with a high potential for abuse and no medical purpose including heroin, LSD, phencyclidine, MDMA or "ecstasy", synthetic marijuana, cathinones and "bath salts", and numerous chemically designed hallucinogens. Schedule 2 drugs have a high abuse potential, but have a medically accepted indication, and include most opioids like morphine and oxycodone, as well as prescribed stimulants. Commonly abused prescribed and illicit opioids are listed in Table 11.1.

Table 11.1 Generic name, trade name, and street name of commonly abused opioids

Generic name	Trade name	Street name
Codeine	Tylenol 3	Cody, Captain, Schoolboy, Syrup
Morphine	MS Contin, Avinza, Depodur, Duramorph, Infumorph, Astramorph, Kadian	M, Monkey, Good Fella, Miss Emma, Morph
Heroin (illicit drug)	N/A	H, White, Horse, Junk, Dope, Black, Brown Sugar, Tar
Oxycodone	Percocet, Percodan, Oxycontin, Roxicodone	Oxys, Cotton, Orange County, Killers, OC
Hydrocodone	Vikodin, Lorcet, Lortab, Hycodan	Vics, Hydros, Lorris, Watsons
Hydromorphone	Dilaudid, Exalgo	Hospital Heroin, Dust, Juice, Dillies, M2 s
Oxymorphone	Opana	Blue Haven, Octagons, Biscuits, Pink Lady
Meperidine	Demerol	Dust, Juice, Demmies
Tramadol	Ultram, Ultracet	Trammies, Chill pills, Ultras
Fentanyl	Sublimaze, Duragesic (transdermal)	Apache, TNT, China girl, China White, Tango and Cash
Methadone	Methadone, Dolophine	Chocolate chip cookies, Fizzies, Saliva, Wafers
Buprenorphine	Buprenex, in combination with naloxone – Suboxone, Zubsolv, Bunavail, Cassipa	Box, Stops, Subs

Pharmacology of Opioids

Three distinct types of opioid receptors are found in the nervous system: mu, kappa, and delta. Other receptors involve the opioid system, including nociceptive receptors, and the zor receptor. The most well-known three types are classical seven-transmembrane domain, G-protein-coupled receptors. Three types of endogenous opioids – beta-endorphin, enkephalins, and dynorphins – have a degree of selectivity for mu, kappa, and delta receptors, respectively. Exogenous opioids act primarily as agonists or partial agonists at mu receptors. The endogenous opioid system plays an important role in response to pain, stress-regulation involving hypothalamic-pituitary-adrenal axis, as well as reproductive, gastrointestinal, cardiovascular, and pulmonary function [2].

Heroin is a potent agonist of mu-opioid receptors; it has a half-life of 30 minutes but a duration of action of 4–5 hours due to active metabolites, including morphine. Heroin is more lipid soluble than other opioids, allowing it to rapidly cross the blood-brain barrier (within 15–20 seconds) and to reach high levels in the brain. Heroin is metabolized to 6-monoacetylmorphine (6-MAM), a metabolite specific to heroin, detectable on urine testing.

Epidemiology of Opioid Use Disorder

From 1999 to 2017, almost 400,000 people died from an overdose involving any opioid, including prescription and illicit opioids. The total number of U.S. opioid-related overdose deaths has reached 47,600 in 2017 [14]. Increased prescription of opioid medications contributed to widespread misuse of both prescription and non-prescription opioids. New synthetic opioids, most of which are fentanyl analogs in combination with heroin or non-opioid drugs, pose a public health threat. Heroin (diacetylmorphine) remains the most popular illicit opiate, though use of fentanyl has increased. Although the majority (80%) of people who use heroin first misused prescription opioids [4], only a fraction of people who abuse pain relievers switch to heroin use [5].

Opioid use disorder is often associated with other substance use disorders, especially those involving tobacco, alcohol, cannabis, stimulants, and benzodiazepines, which are often taken to reduce symptoms of opioid withdrawal or craving for opioids, or to enhance the effects of administered opioids. Additional consequences of the opioid crisis include a rising incidence of infants born with neonatal abstinence syndrome (NAS) because their mothers used these substances during pregnancy, and increased spread of infectious diseases, including HIV and hepatitis C.

Diagnosis of Opioid Use Disorder

Opioid use disorder is defined by the Diagnostic and Statistical Manual 5 as two or more of the following within the same 12-month period [1]:

- Using larger amounts of opioids or over a longer period than was intended.
- Persistent desire to cut down or unsuccessful efforts to control use.
- Great deal of time spent obtaining, using, or recovering from use.
- Craving, or a strong desire or urge to use substance.
- Failure to fulfill major role obligations at work, school, or home due to recurrent opioid use.
- Continued use despite recurrent or persistent social or interpersonal problems caused or exacerbated by opioid use.
- Giving up or reducing social, occupational, or recreational activities due to opioid use.
- Recurrent opioid use in physically hazardous situations.
- Continued opioid use despite physical or psychological problems caused or exacerbated by its use.
- Tolerance (marked increase in amount; marked decrease in effect).
- Withdrawal syndrome as manifested by cessation of opioids or use of opioids (or a closely related substance) to relieve or avoid withdrawal symptoms.

Tolerance and withdrawal criteria are not considered to be met for those taking opioids solely under appropriate medical supervision.

Severity of opioid use disorder is categorized as mild (presence of 2–3 symptoms), moderate (4–5 symptoms), or severe (6 or more symptoms).

Remission of opioid use disorder is categorized as:

- In early remission: where none of the criteria for opioid use disorder have been met for at least 3 months but for less than 12 months (with the exception of craving, or a strong desire or urge to use opioids), but full criteria for opioid use disorder were previously met.
- In sustained remission: where none of the criteria for opioid use disorder have been met at any time during a period of 12 months or longer (with the exception of craving, or a strong desire or urge to use opioids), but full criteria for opioid use disorder were previously met.

Specifiers include if the individual is in an environment where access to opioids is restricted and whether an individual with opioid use disorder is on maintenance therapy, such as taking a prescribed agonist (methadone), partial agonist (buprenorphine), agonist/antagonist (buprenorphine/naloxone), or a full antagonist (naltrexone).

Evaluation

Diagnostic Interview: See Chap. 2

Physical examination: Cutaneous signs: needle puncture marks over veins, especially in the antecubital area, back of the hands and forearms, but also on the neck, under the tongue, between the toes; “tracks” – hyperpigmented linear scars located

along veins; hand edema; thrombophlebitis; abscesses and ulcers; ulceration or perforation of the nasal septum; chelosis; signs of opioid withdrawal: piloerection, pupil dilation, sweating, yawning, rhinorrhea, lacrimation, fever (uncommon).

Laboratory tests: A standard opiate immunoassay test will detect the use of morphine, codeine, hydrocodone, oxycodone and heroin, though it has less sensitivity for oxycodone and hydrocodone. Synthetic opioids such as meperidine, fentanyl, methadone, and buprenorphine will not be detected and require their own test. Oxycodone and hydrocodone also have their own tests.

Opioid Intoxication and Overdose

Diagnostic criteria for opioid intoxication [1]:

A. Recent use of an opioid.
B. Clinically significant problematic behavioral or psychological changes (e.g., initial euphoria followed by apathy, dysphoria, psychomotor agitation or retardation, impaired judgment) that developed during or shortly after, opioid use.
C. Pupillary constriction (or pupillary dilation due to anoxia from severe overdose) and one (or more) of the following signs or symptoms developing during or shortly after, opioid use:
   (a) Drowsiness or coma.
   (b) Slurred speech.
   (c) Impairment in attention or memory.
D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance.

The level of tolerance to opioids can have a significant effect on an individual's risk of opioid overdose. Tolerance to respiratory depression is lower than tolerance to euphoric effects, which explains why overdose often occurs even among "experienced" opioid users. Recently, detoxified patients or people with long period of abstinence (recently released or received treatment with opioid antagonists) are at higher risk for nonfatal overdose.

Acute opioid use significantly reduces the responsiveness of the brainstem respiratory centers to carbon dioxide, and reduces peripheral chemoreceptor response to hypoxia, thought largely to be mediated by mu opiate receptors.

Diagnosis of opioid overdose:

(a) Classic "triad": coma, pinpoint pupils, respiratory depression (respiratory rate < 12/min),
(b) History of opioid use (ask about drug, amount and time of last use). Polydrug use (high mortality if combined opioids and benzodiazepines, alcohol, or cocaine) may indicate the need for additional therapy (e.g., flumazenil to reverse benzodiazepine effect),

(c) Use of collateral information,
(d) Circumstantial evidence of opioid use (i.e., needle marks or cellulitis),
(e) Laboratory tests: toxicology screens for opioids and other drugs, rule out hypoglycemia, acidosis, electrolyte abnormalities.

Atypical presentation and unusual complications may be the result of contamination of drugs of abuse – substances used to "cut" street drugs, including dextromethorphan, lidocaine, scopolamine, and levamisole.

Management of opioid overdose involves administration of an opioid antagonist to reverse the effects. Naloxone hydrochloride (Narcan nasal spray, Evzio – autoinjector), a pure opioid antagonist, can effectively reverse the CNS effects of opioid intoxication and overdose. Naloxone is labeled for intravenous, intramuscular, subcutaneous, and intranasal use. Initial dose 0.4–0.8 mg may be repeated at 2–3 minute intervals. Overdose with opioids that are more potent and have high receptor binding affinity (such as fentanyl) or longer acting (such as methadone) may require higher doses of naloxone given over longer periods of time. If the patient does not respond to multiple doses of naloxone, consider alternative causes – polydrug intoxication, medical causes (hypoglycemia, acidosis, electrolyte abnormalities, head trauma, subarachnoid hemorrhage).

Opioid Withdrawal

Clinical phenomena associated with opioid withdrawal include physiological rebound of symptoms caused by opioid intoxication. The severity of opioid withdrawal varies with the specific opioid used, route of administration, the dose and duration of drug use. The half-life of the drug determines the onset and the duration of acute withdrawal. Thus, withdrawal may begin 4 to 6 hours after the use of heroin and subside substantially within 5–7 days. With methadone withdrawal, in contrast, the onset of withdrawal may be delayed up to 36 hours after the last use of methadone, but the symptoms do not subside for 14–21 days. Intermittent drug use usually does not cause severe withdrawal. Although opioid withdrawal generally includes no life-threatening complications in adults, it causes marked discomfort, prevents many patients from entering treatment, and often is a factor in continuation of opioid use to relieve suffering. A protracted abstinence syndrome that can last months has been described, which may include continuous craving, insomnia, fatigue, dysphoria, and irritability, all of which increase the likelihood of relapse [3].

Diagnostic criteria for opioid withdrawal [1]:

A. Presence of either of the following:
   1. Cessation of (or reduction in) opioid use that has been heavy and prolonged (i.e., several weeks or longer).
   2. Administration of an opioid antagonist after a period of opioid use.
B. Three (or more) of the following, developing within minutes to several days after Criterion A:

Dysphoric mood, nausea or vomiting, muscle aches, lacrimation or rhinorrhea, pupillary dilation, piloerection, or sweating, diarrhea, yawning, fever, insomnia.

C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The signs and symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

Several clinical tools are available to assess the severity of opioid withdrawal. Ones of the most widely used are the Clinical Opioid Withdrawal Scale (COWS), designed to be administered by a clinician, and Subjective Opiate Withdrawal Scale (SOWS), designed to be completed by the patient [9]. Both scales quantify severity of opioid withdrawal and monitor these symptoms over time. Opioid withdrawal can be managed in inpatient or outpatient settings. Several factors, including severity of withdrawal, presence and severity of underlying medical and psychiatric comorbidities, failure to complete outpatient detoxification in the past, availability of social supports, and access to methods of detoxification may determine the treatment approach (slow vs. rapid detoxification) and a choice of the treatment setting.

Management of opioid withdrawal involves a combination of general supportive measures (safe environment and adequate nutrition) and specific pharmacologic therapies such as use of full (methadone) or partial opioid agonists (buprenorphine), alpha-2 adrenergic agonists (clonidine, guanfacine and lofexidine (Lucemyra)), and medications providing symptomatic relief (nonsteroidal anti-inflammatory agents, ondansetron, dicyclomine, loperamide, benzodiazepines, trazodone, etc.). *Medical detoxification without following maintenance treatment has very limited effect in relapse prevention.*

Methadone, a long-acting full mu-opioid agonist, effectively controls opioid withdrawal and reduces craving for opioids. Use of methadone has been restricted to inpatient settings or specialized licensed outpatient drug treatment programs (OTPs). Initially, methadone may be given, up to a total of 30–40 mg over the first 24 hours, in 5- to 10-mg increments. Dose adjustment can then be made on the basis of objective signs of opioid withdrawal rather than on subjective complaints alone. Methadone tapering can be accomplished in 5–7 days in inpatient setting, whereas outpatient detoxification is often extended to minimize withdrawal symptoms and to decrease the likelihood of relapse.

Buprenorphine is a high-affinity, long-acting partial mu-opioid agonist with better safety profile when compared to methadone, that is effective for treatment of opioid withdrawal and maintenance treatment of OUD [9]. Buprenorphine may displace opioid agonists from mu-opioid receptors and precipitate opioid withdrawal in patients with recent opioid usage. It has been suggested that inducting patients dependent on short-acting opioids (i.e., heroin) should occur after the emergence of mild to moderate withdrawal symptoms (6–12 hours after the last heroin use). A typical approach is to administer buprenorphine 2–4 mg sublingually, and another 2- to 4-mg dose of buprenorphine approximately 1 hour later, depending on the

patient's comfort level, with a total of 8–12 mg of buprenorphine to sufficiently relieve withdrawal symptoms. Buprenorphine taper may be successfully completed in 5–7 days in inpatient setting, whereas outpatient detoxification is often gradual and may take 2–8 weeks.

Both opioids and alpha-2 adrenergic agonists can suppress activity of the locus coeruleus, a major noradrenergic center in the brain which is hyperactive during opioid withdrawal. Clonidine, an alpha-2 adrenergic agonist, an antihypertensive, has been used to facilitate opioid withdrawal in both inpatient and outpatient settings. Clonidine has mild analgesic properties and at dosages of 0.6–1.2 mg/day reduces many of the autonomic components of the opioid withdrawal syndrome, although craving, muscle aches, insomnia, and irritability are not well suppressed, but can be ameliorated by other adjunct treatments. Benzodiazepines can be used short-term to treat insomnia and muscle aches, but should be given with caution given their own misuse potential and interaction with opioids, especially in the outpatient setting.

Clonidine has some advantages over the use of opioid agonists: it has no addictive properties, is available to general physicians, and facilitates transition to maintenance treatment with opioid antagonists. Sedation and dizziness from orthostatic hypotension have been reported as the most common side effects of clonidine. Patients should be cautioned about driving and operating equipment during the first few days. History of psychosis, cardiac arrhythmias, pregnancy, and use of tricyclic antidepressants within 3 weeks precludes use of clonidine [2]. In May of 2018 the US Food and Drug Administration (FDA) approved a non-opioid agent, lofexidine hydrochloride (Lucemyra) for the mitigation of withdrawal symptoms. Lofexidine is a selective alpha-2 adrenergic agonist, an analogue of clonidine producing less hypotension and sedation.

Agents other than opioid agonists and alpha-2 adrenergic agonists have been investigated for treatment of opioid withdrawal. Various alternatives to current detoxification strategies, including the use of N-methyl-D-aspartate (NMDA) receptor antagonist memantine, 5HT-1A partial agonist buspirone, gabapentin, tramadol, ibogaine, acupuncture, and others require further study. Anesthesia-assisted ultrarapid opioid detoxification has revealed little benefit while leading to significant adverse events [2].

Opioid Maintenance Treatment

There are two main modalities for the treatment of OUD: psychotherapy (discussed elsewhere) and pharmacotherapy. Three pharmacological agents were approved by the FDA for the treatment of OUD: buprenorphine, methadone, and naltrexone. All three of these treatments have been demonstrated to be safe and effective in combination with counseling and psychosocial support. There is no maximum recommended duration of maintenance treatment, and for some patients, treatment may continue indefinitely. The goals of treatment include prevention or reduction of medical, psychiatric and other consequences of OUD and improvement of patient's functioning, quality of life, and overall well-being [5].

Opioid Agonists

Treatment with an opioid agonist – methadone or buprenorphine – at an adequate dose suppresses craving and withdrawal symptoms, attenuates the euphoric effects of illicit opioids due to cross-tolerance, allows patients to improve psychosocial functioning, and reduces criminal activity and transmission of infectious diseases. Oral or sublingual route of administration leads to a relatively slow rate of increase in plasma level and thus is less euphorigenic and reinforcing. Longer half-life allows to prevent withdrawal and stabilize fluctuations in mood and level of consciousness found with use of short-acting opioids.

Methadone has proven efficacy for reducing illicit opioid use and for reducing the mortality and morbidity associated with OUD in numerous studies since the methadone was approved for use in the United States in 1947. Both methadone and buprenorphine are included in The World Health Organization List of Essential Medicines, the most effective and safe medicines needed in a health system [8]. Methadone for maintenance treatment of OUD is only available in specialized and licensed OTP programs. Methadone as a full mu-opioid receptor agonist carries a higher risk of abuse, can cause potentially fatal respiratory depression or lethal overdose in accidental ingestion. Methadone use is also associated with QT interval prolongation and serious arrhythmia (torsades de pointes), particularly at higher doses. Providers should be aware of substantial inter-individual pharmacokinetic variability and numerous drug interactions. Most significant medication interactions with methadone are presented in Table 11.2.

Table 11.2 Medication interactions with methadone [6, 7]

Medications that may reduce methadone clearance and increase risk of potential toxicity and cardiac arrhythmia (torsades de pointes)	Antiarrhythmics: amiodarone, diltiazem, verapamil, quinidine Macrolide antibiotics: clarithromycin, erythromycin, ciprofloxacin Antifungals: fluconazole, ketoconazole, voriconazole, terbinafine SSRI: sertraline, paroxetine, fluvoxamine Urinary alkalinizers (sodium bicarbonate decreases methadone excretion by kidneys) Other: Disulfiram, Dihydroergotamine, Ethanol, Moclobemide, Metronidazole, grapefruit juice
Medications that may accelerate metabolism of methadone and increase risk of opioid withdrawal	Antiepileptics: carbamazepine, phenobarbital, phenytoin Antiretrovirals: efavirenz, nevirapine, darunavir/ritonavir, lopinavir/ritonavir, nelfinavir, tipranavir/ritonavir Other: rifampin, St. John's wort
Medications associated with QT interval prolongation	Anesthetics, muscle relaxants, antiemetics (ondansetron, granisetron), antipsychotics (chlorpromazine, ziprasidone, aripiprazole, quetiapine), SSRI (citalopram, fluoxetine, paroxetine, sertraline), tricyclic antidepressants, some anticholinestherase inhibitors
Pharmacodynamic synergistic interaction resulting in increased sedation and potentially lethal respiratory depression	Alcohol, benzodiazepines, barbiturates, opioids, and other CNS depressants

Slow methadone detoxification is used for termination of methadone maintenance treatment to avoid long residual withdrawal symptoms from methadone withdrawal. Patients who desire to become drug-free, should be tapered off methadone slowly over a 3- to 6-month period or longer.

Buprenorphine has a unique pharmacological and safety profile which makes it an attractive treatment for patients with OUD as well as for medical professionals treating them. As a partial agonist at the mu-opioid receptor it has very high affinity and low intrinsic activity, which means it will displace full opioid agonists without stimulating the receptor at full strength. It has lower abuse potential comparing to methadone, lower level of physical dependence, less withdrawal discomfort, and a ceiling effect at higher doses meaning buprenorphine is less likely to cause fatal respiratory depression in comparison with a full opioid agonist. As any drug stimulating mu-opioid receptor, buprenorphine is a subject for abuse and diversion. To decrease the potential for abuse the buprenorphine/naloxone combination has been developed. Sublingual naloxone has relatively low bioavailability, however, in case of diversion and injectable use of the combination product, parenteral naloxone which has good bioavailability will precipitate withdrawal syndrome [9]. Buprenorphine is metabolized by CYP 450 3A4; therefore, agents that inhibit or induce CYP 3A4 enzyme can increase or reduce plasma concentration of buprenorphine. In therapeutic dose buprenorphine does not cause QT interval prolongation. Buprenorphine can cause respiratory depression if co-administered with other CNS depressants, i.e., alcohol, benzodiazepines, etc. [6] A buprenorphine implant (Probuphine), approved by the FDA in 2016, provides a low, steady dose of the medication for 6 months. The implant is intended for use only in patients who have first achieved clinical stability with sublingual buprenorphine at a daily dose of 8 mg or less. The implant requires a minor surgical procedure for both insertion and removal. In case of transferring patients from methadone to buprenorphine, the methadone dose should be reduced to 30–40 mg with the last methadone dose 24–48 hours prior to buprenorphine induction.

Opioid Antagonists

Naltrexone, a long-acting orally available mu-opioid antagonist, provides blockade of mu-opioid receptors, thus blocking the reinforcing properties of opioids, which theoretically makes it an ideal maintenance agent for patients with OUD. Poor adherence and increased risk of overdose after discontinuation of treatment significantly limited the use of *oral* naltrexone for OUD. Nevertheless, in the situation when the medication use can be supervised, and for certain highly motivated subsamples of patients with OUD, such as health care professionals, business executives, pilots, commercial drivers, probation referrals, for whom there is an external incentive to comply with naltrexone therapy and to remain opioid abstinent, naltrexone has been very effective. As an example, naltrexone has been a routine adjunct for the treatment of anesthesiologists who are addicted to opioids [3]. In 2010, an extended-release injectable naltrexone (XR-NTX) formulation was

FDA-approved for the prevention of relapse to opioid dependence following opioid detoxification as part of an individualized comprehensive management program that includes psychosocial support [10].

This long-acting formulation can be given in a wide range of clinical settings, including primary care and criminal justice systems. Patients treated with XR-NTX have less treatment dropout, lower rates of opioid use, and reduced craving, as compared with patients treated with placebo [11]. Persons on probation or parole who were randomly assigned to an open-label treatment with XR-NTX compared with treatment as usual had significantly lower rates of relapse, longer relapse-free survival, lower rates of heroin use, and fewer overdoses over a 24-week treatment period, with a loss of effect seen at 28 and 54 weeks after the end of treatment [10]. Recent studies directly comparing the efficacy of XR-NTX and buprenorphine/naloxone show that among patients who successfully initiated treatment with medications, treatment outcomes were comparable [12].

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

General characteristics of agents used for maintenance treatment of OUD and treatment principles are summarized in Table 11.3.

Pregnant Women

Pregnant women with OUD are more likely to seek prenatal care late in pregnancy, miss appointments, experience poor weight gain, or exhibit signs of withdrawal or intoxication. The fluctuating levels of opioids in the blood of mothers misusing opioids expose the fetus to repeated periods of withdrawal, which can also harm the function of the placenta and increase the risk of intrauterine complications, preterm labor, and fetal death [13]. Pregnant women are also at risk of untreated maternal infections such as HIV, malnutrition and poor prenatal care, and dangers conferred by drug-seeking lifestyle, including violence and incarceration. Although there are no medications approved by FDA for treatment of OUD in pregnant women, methadone remains the standard of care for pregnant women with OUD. Methadone maintenance enhances the ability of the woman to participate in prenatal care and addiction treatment. A stable methadone dose reduces the fluctuations in maternal opioid levels that can occur with illicit opioid use, and this stabilization reduces stress on the fetus. Treatment with methadone should be initiated as early as possible. Providers should be aware that with advancing gestational age, plasma levels of methadone progressively decrease and clearance increases, therefore, increased or divided doses are often needed. After child birth, doses may need to be adjusted. During pregnancy, the use of buprenorphine monoproduct (Subutex) is preferred to prevent prenatal naloxone exposure, which may precipitate withdrawal and potentially cause maternal and fetal hormonal changes. Pharmacokinetics of buprenorphine does not significantly change during pregnancy, and the need to adjust dosing of buprenorphine

Table 11.3 Comparison of opioid agonists and antagonists used for maintenance treatment of OUD

	Full opioid agonist	Partial opioid agonist/antagonist	Opioid antagonist
Generic (trade) name	Methadone (Dolophine)	Buprenorphine (Subutex) Buprenorphine/naloxone (Suboxone, Zubsolv, Bunavail, Cassipa)	Extended-release injectable naltrexone (Vivitrol)
Mechanism of action	Mu-opioid receptor agonist, weak N-methyl-D-aspartate (NMDA) receptor antagonist	Mu-opioid receptor partial agonist, kappa-opioid receptor antagonist	Mu-opioid receptor antagonist, partial kappa-opioid receptor agonist
Pharmacokinetics	Extensively metabolized by CYP 3A4, 2B6, 2D6, and 2C19. Autoinduction of metabolism. Elimination half-life is highly variable, from 12–150 hours	Metabolized by CYP 3A4 and 2C8. Elimination half-life of sublingual buprenorphine is 24–42 hours	Metabolized by dihydrodiol dehydrogenase and not by the CYP450 system. Elimination half-life of injectable naltrexone is 5–10 days
Adverse effects	Sedation, dizziness, orthostatic hypotension, headache, constipation, sweating, nausea, vomiting, reduced libido, erectile dysfunction, urinary retention, dry mouth, peripheral edema, respiratory depression, QT-interval prolongation, cardiac arrhythmias, coma	Headache, constipation, nausea, sweating, orthostatic hypotension, oral hypoesthesia, peripheral edema	Nausea, headache, decreased appetite, pharyngitis, anxiety, insomnia, diarrhea, liver function abnormalities (<1%), injection site reactions (pain, tenderness, induration, swelling, erythema, or bruising)
Initial dose	10–30 mg, do not exceed 30 mg, may be increased in increments of 5-10 mg	2–4 mg, may be increased in increments of 2–4 mg	380 mg deep intramuscular injection in the gluteal muscle
Usual dosage	60–120 mg daily	8–24 mg daily	380 mg every 4 weeks
Risk of overdose	Increased risk of overdose and death during the initial 2 weeks of methadone induction. High genetic variability in metabolism rate. Concomitant use of medications interfering with methadone metabolism or sedatives (alcohol, benzodiazepines) increases risk of overdose	Partial agonist properties produce a ceiling effect and reduce the risk of overdose. Less risk of QT interval prolongation	Increased risk of overdose on illicit opioids if treatment was interrupted

Induction requirements	No	Patient must experience mild to moderate opiate withdrawal before taking the first dose to reduce the risk of precipitated withdrawal. Induction requires physician observation	Absence of physical dependence from opiate agonists: at least 7 days between the last dose of heroin and the first dose of naltrexone, or 10–14 days between the last dose of methadone or buprenorphine/naloxone and the first dose of naltrexone; naloxone challenge may be useful
Psychosocial treatment	Required	Recommended	Recommended
Habit forming/risk of diversion	Yes	Yes	No
Frequency of visits	Determined by federal guidelines; daily visits during stabilization	1–2 times a week during stabilization, then biweekly or monthly	No specific requirements; injections given monthly
Barriers for treatment	Stigmatization Requires specialized setting – Outpatient treatment program Adverse effects and interaction with other agents Fear of physical withdrawal upon treatment cessation	Patients unable to tolerate withdrawal symptoms prior to induction Prescription rights limited to certified physicians through the drug addiction treatment act (DATA) Fear of physical withdrawal upon treatment cessation	Difficulty initiating treatment Low penetration into formularies Limited knowledge among professionals
Transition to other medication	To buprenorphine: Patients on low dose of methadone (30–40 mg or less), wait until develop mild to moderate withdrawal To naltrexone: Stop methadone for up to 14 days to avoid withdrawal; naloxone challenge may be useful	To methadone: no required time delay To naltrexone: 7–14 days between the last dose of buprenorphine and the first dose of naltrexone to avoid precipitated withdrawal; naloxone challenge may be useful	Switching from naltrexone to full agonist or partial agonist is less complicated, there is no risk of precipitated withdrawal. Consider lower initial dose of full agonist or partial agonist
Discontinuation of treatment	Slow taper over several months; abrupt discontinuation causes prolonged opiate withdrawal	Slow taper over several weeks to months; abrupt discontinuation causes opiate withdrawal	Taper not necessary

during pregnancy is less than that of methadone. Flexible twice a day dosing may reduce withdrawal symptoms and craving to use illicit drugs. A number of studies demonstrated strong evidence for improved outcomes with buprenorphine comparing with methadone, including lower risk of preterm birth, greater birth weight, and less severe neonatal abstinence syndrome (NAS) [16, 17]. Mothers receiving methadone and buprenorphine monoproduct for the treatment of opioid use disorders should be encouraged to breastfeed as long as the mother is not using other drugs.

Review Questions

1. A 47-year-old woman with a long history of treatment refractory depression presents to a methadone clinic and is recommended to start methadone for her opioid use disorder, but she cannot remember the name of her depression medication. Which medication requires two-week washout period prior to methadone induction?
   A. Desipramine
   B. Chlorpromazine
   C. Fluvoxamine
   D. Phenelzine

   Correct Answer: D. Phenelzine

   Explanation: Methadone as well as meperidine, dextromethorphan, and tramadol appear to be weak serotonin re-uptake inhibitors and have all been involved in serotonin toxicity reactions with MAOIs (including some fatalities). Morphine, codeine, oxycodone, and buprenorphine are known not to be SRIs, and do not precipitate serotonin toxicity with MAOIs [15]
2. A 17-year-old male presents to your clinic seeking buprenorphine for his opioid use disorder. He reports using the medication illicitly several times to treat opioid withdrawal, and reluctantly admits to trying to use it to get high once, but says that it "didn't work very well for that." A "ceiling effect" of the mu opioid receptor partial agonist buprenorphine means that:
   A. At low doses buprenorphine acts as an opioid antagonist and does not cause euphoria
   B. Buprenorphine at higher doses is less likely to cause fatal respiratory depression in comparison with a full opioid agonist
   C. When abruptly stopped, buprenorphine causes only mild opioid withdrawal
   D. Buprenorphine as a mixed agonist/antagonist has low addictive potential, and when injected, buprenorphine precipitates opioid withdrawal

   Correct answer: B.

   Explanation: Buprenorphine as a partial mu-opioid receptor agonist has very high affinity and low intrinsic activity, which means it will occupy the receptor without stimulating it at full strength to produce respiratory depression. [9]

3. A 27-year-old, 24-week pregnant woman presents to the methadone clinic complaining of nausea, diarrhea, runny nose, and muscle aches that peak in the morning before she comes to the clinic. For pregnant women with OUD on methadone maintenance treatment during the second trimester, the dose of methadone most likely will be:
   A. Reduced to prevent neonatal abstinence syndrome
   B. Increased to control opioid withdrawal and prevent relapse
   C. Unchanged to prevent the fetus from developing withdrawal syndrome
   D. Reduced to avoid cardiovascular complications

   Correct answer: B.

   Explanation: Increased fluid volume and metabolism rate during pregnancy will affect distribution and accelerate metabolism of methadone, which may lead to precipitated opioid withdrawal and require dose adjustment [13].
4. A 57-year-old anesthesiologist with opioid use disorder has been taking oral naltrexone while seeking to reinstate his medical license. He finds taking the medication every day a reminder of when he had to take opioids every day to prevent withdrawal, and asks about extended-release naltrexone. Which statement is correct regarding the extended-release injectable naltrexone (XR-NTX)?
   A. In 1990, XR-NTX was FDA-approved for maintenance treatment of opioid use disorder
   B. XR-NTX demonstrated worse adherence to treatment comparing to oral naltrexone
   C. XR-NTX is not primarily metabolized by CYP 450 3A4 enzymes
   D. XR-NTX requires a special license to prescribe

   Correct answer: C.

   Explanation: Naltrexone is extensively metabolized in humans. Production of the primary metabolite, 6 β-naltrexol, is mediated by dihydrodiol dehydrogenase, a cytosolic family of enzymes in the liver. The cytochrome P450 system is not involved in naltrexone metabolism. Naltrexone and its metabolites are also conjugated to form glucuronide products [7].

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed (DSM-5). Arlington: American Psychiatric Association; 2013.
2. Galanter M, Kleber H, Brady K. The American Psychiatric Publishing Textbook of Substance Abuse Treatment. 4th ed. American Psychiatric Publishing, Inc. 2007.
3. Fiellin D, Miller S, Saitz R. The ASAM Principles of Addiction Medicine. 5th ed. Wolters Kluwer; 2014.
4. Muhuri PK, Gfroerer JC, Davies MC. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. CBHSQ Data Rev. August 2013.
5. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. J Addict Med. 2015;9:358–67.

6. McCance-Katz E, Sullivan L, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. Am J Addict. 2010;19(1):4–16.
7. Saber-Tehrani A, Bruce R, Altice F. Pharmacokinetic drug interactions and adverse consequences between psychotropic medications and pharmacotherapy for the treatment of opioid dependence. Am J Drug Alcohol Abuse. 2011;37:1–11.
8. WHO Model List of Essential Medicines (19th List) (PDF). World Health Organization. April 2015. Archived (PDF) from the original on 13 December 2016. Retrieved 8 December 2016.
9. Center for Substance Abuse Treatment. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 07-3939. Rockville: Substance Abuse and Mental Health Services Administration; 2004.
10. Bisaga A, Mannelli P, Sullivan M, Vosburg S, Compton P, Woody G, Kosten T. Antagonists in the medical management of opioid use disorders: historical and existing treatment strategies. Am J Addict. 2018;27:177–87.
11. Nunes E, Krupitsky E, Ling W, Zummo J, Memisoglu A, Silverman B, Gastfriend D. Treating opioid dependence with injectable Extended-Release Naltrexone (XR-NTX): who will respond? J Addict Med. 2015;9:238–43.
12. Lee J, Nunes E, Novo P, Bachrach K, Bailey G, Bhatt S, Farkas S, Fishman M, Gauthier P, Hodgkins C, King J, Lindblad R, Liu D, Matthews A, May J, Peavy K, Ross S, Salazar D, Schkolnik P, Shmueli-Blumberg D, Stablein D, Subramaniam G, Rotrosen J. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet. 2018;91(10118):309–18.
13. Kaltenbach K, Berghella V, Finnegan L. Opioid dependence during pregnancy. Effects and management. Obstet Gynecol Clin North Am. 1998;25(1):139–51.
14. Centers for Disease Control and Prevention. National Vital Statistics System Provisional counts of drug overdose deaths as of 8/6/2017 National Center for Health Statistics, Centers for Disease Control and Prevention; 2017.
15. Gillman PK. Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. Br J Anesth. 2005;95(4):434–41.
16. Tran T, Griffin B, Stone R, Vest K, Todd T. Methadone, buprenorphine and naltrexone for the treatment of opioid use disorder in pregnant women. Pharmacotherapy. 2017;37(7):824–39.
17. Zedler B, Mann A, Kim M, Amick H, Joyce A, Murrelle E, Jones H. Buprenorphine compared with methadone to treat pregnant women with opioid use disorder: a systematic review and meta-analysis of safety in the mother, fetus and child. Addiction. 2016;111:2115–28.

Stimulants: Caffeine, Cocaine, Amphetamine, and Other Stimulants

12

Jeffrey J. DeVido

High-Yield Review Points

- Caffeine's psychostimulatory effects are generally less than that of classical psychostimulants, and its effects are the result of A_1 and A_{2A} adenosine receptor antagonism.
- The DSM-5 allows for formal diagnoses of Stimulant Intoxication, Stimulant Withdrawal, Other Stimulant-Induced Disorder, Unspecified Stimulant-Related Disorder, and Stimulant Use Disorder (addiction) with the categories of stimulants being amphetamine-type substances, cocaine, and other or unspecified stimulants (e.g., *khât*, cathinone derivatives). The DSM-5 also allows for Caffeine-Induced Disorders (e.g., anxiety and panic) as well as a characteristic Caffeine Withdrawal Syndrome.
- Cocaine is a potent reuptake blocker of catecholamines, while amphetamine and most amphetamine-type stimulants both block reuptake *and* function as transporter substrates that cause a greater release of intracellular catecholamines.
- There are no FDA-approved pharmacotherapies for cocaine use disorder and for amphetamine and amphetamine-type stimulant use disorders, despite trials of many potential different pharmacotherapies for this purpose.
- Psychosocial and behavioral therapies remain the mainstay of treatment for cocaine use disorder and for amphetamine and amphetamine-type stimulant use disorders, with cognitive behavioral therapies and contingency management approaches having demonstrated efficacy.

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Introduction

Stimulants is a term that describes a diverse range of naturally occurring and synthetic substances that are used for medical and non-medical purposes. Naturally occurring stimulants have been consumed for millennia and are found in various species of plants grown naturally and cultivated throughout the world including coca (cocaine), *khât* (cathinone), ephedra (ephedrine and pseudoephedrine), tea and coffee (caffeine), and tobacco (nicotine). Synthetic stimulants are legion, and include amphetamine, methylphenidate, methamphetamine, methylenedioxymethamphetamine (MDMA), modafinil and r-modafinil, benzphetamine, diethylpropion, mazindol, phendimetrazine, phenmetrazine, phentermine, and the cathinone derivatives ephedrone and mephedrone. While many stimulants are ingested orally, they are also widely ingested (both licitly and illicitly) via inhalation, injection, and intranasal, topical, and transrectal routes of administration.

Medical uses of stimulants are myriad and include the treatment of attention-deficit hyperactivity disorder (ADHD), nasal sinus congestion, migraine headaches, sleep disorders, obesity, altitude sickness, as well as topical anesthesia. Stimulants are also used in improving cognitive performance and for wakefulness enhancement.

As a class, stimulants act pharmacologically in both the central and peripheral nervous systems where they primarily enhance the transmission of the catecholamine neurotransmitters norepinephrine and dopamine, creating the characteristic hedonic, reinforcing and sympathomimetic effects attributed to stimulants: e.g., euphoria, increased libido, decreased appetite, increased attention and wakefulness, tachycardia and hypertension, and hyperthermia. Stimulants can also secondarily affect additional neurotransmitter systems (adenosine, serotonergic, and alpha and beta adrenergic systems, and neuronal sodium channel systems; they also inhibit monoamine oxidase function), which contribute to the variety of physiological and psychiatric effects attributed to stimulants.

The Diagnostic and Statistical Manual, fifth Edition (DSM-5), describes several disorders related to stimulants, which are divided into the following rubrics: intoxication, withdrawal, use disorder (addiction), other induced disorders, and unspecified stimulant-related disorders [1]. In this chapter, the main focus will be on intoxication, withdrawal, and use disorders related to stimulants. When relevant, other induced disorders and unspecified stimulant-related disorders will be highlighted, but it is sufficient to understand more broadly that other induced disorders and unspecified stimulant-related disorders represent the following: (1) other induced disorders are syndromes that resemble primary psychiatric disorders; however, the cause is stimulant related (e.g., caffeine-induced anxiety disorder, methamphetamine-induced psychotic disorder) and (2) unspecified stimulant-related disorders are syndromes wherein stimulant use results in clinically significant distress and/or impairment without meeting full diagnostic criteria for intoxication, withdrawal, or use disorder (e.g., unspecified caffeine-related disorder) [1].

Significantly, stimulants have a high potential for non-medical use as well as addiction, and are widely misused for their hedonic and reinforcing effects, temporary cognitive and sexual enhancement, and augmentation of alertness and energy.

It is difficult to definitively pinpoint the proportion of those who use stimulants who will go on to develop a stimulant use disorder (addiction). National surveys of individuals not in treatment and those seeking treatment estimate that 15% to 50%, respectively, of those misusing stimulants will develop characteristics of a use disorder [2, 3]. Factors that increase the likelihood of developing a stimulant use disorder include: using via routes of administration that favor more rapid delivery to the brain (e.g., inhalation, injection), and greater amounts used [4].

Stimulants are also associated with various deleterious psychiatric consequences such as mood disorders, psychosis, aggression, impulse control disorders, and panic attacks. The negative physiologic effects of stimulant misuse are numerous and every organ system can be impacted. Negative psychiatric and physiological consequences result from either direct effect of the stimulant (e.g., the excessive dopamine release and consequent psychosis and movement disorders seen in methamphetamine use), or indirect stimulant effects (e.g., organ ischemia due to vasoconstriction). Additional negative consequences of stimulant misuse include trauma sustained while intoxicated, as well as the full range of social/economic/relational/legal consequences typical of all addictive disorders. While adulteration of illicit stimulant supplies with potentially toxic "fillers" and additives is not new, recent experience supports the increasingly widespread presence of the potent synthetic opioid fentanyl in illicit stimulant supplies, resulting in opioid overdose deaths.

In this chapter, particular focus will be on caffeine, cocaine, and amphetamines. Nicotine and MDMA will be considered in separate chapters. Over-the-counter stimulants and the wakefulness enhancers modafinil and r-modafinil will not be considered further in this chapter.

Caffeine

Caffeine is an alkaloid chemical that is consumed orally through food, drink, and dietary supplements and is present in over 60 different species of plants, such as tea, guarana, cacao, and yerba maté. Recently, caffeine has also become incorporated into cosmetic products under the auspices of facilitating hair growth (with limited preclinical evidence) [5]. Caffeine is the most widely used psychoactive substance in the world, with an estimated 85% of the US population 2 years old and older consuming one or more caffeinated beverages a day [6]. Caffeine use is generally not associated with significant deleterious health consequences when used in moderation, and caffeine ingestion may in fact provide some health benefits by preventing Parkinson's disease, liver cirrhosis, and certain forms of dementia and depression, although the data on these effects are currently inconclusive [7–9].

Caffeine is used medically in conjunction with various analgesics such as acetaminophen and ibuprofen to enhance the pain-mitigating effects of these analgesics, to treat caffeine withdrawal, and to treat apnea in neonates and infants [10, 11]. Outside of medical indications, caffeine is widely consumed to improve alertness and enhance wakefulness and is commonly added in varying amounts to weight loss and energy products, sometimes in conjunction with alcohol.

Endogenous adenosine activity is responsible for escalating sleepiness following periods of prolonged wakefulness and also is implicated in several other aspects of sleep homeostasis. Caffeine's psychomotor-reinforcing effects and hyperarousal are the result of the antagonism of central A_1 and A_{2A} adenosine receptors. Compared to classical psychostimulants such as cocaine and amphetamine, caffeine has comparatively less augmentation effect on dopaminergic and catecholaminergic neurotransmission. Nonetheless, caffeine ingestion increases both systolic and diastolic blood pressures, causes head and neck vasoconstriction as well as bronchodilation, and has diuretic and colonic stimulatory effects [12].

The ubiquity and relative minor health or psychological impact of caffeine make it difficult to pinpoint specific caffeine-related disorders and problems. The Diagnostic and Statistical Manual, fifth Edition (DSM-5), describes Caffeine-Related Disorders as Caffeine Intoxication, Caffeine Withdrawal, Other Caffeine-Induced Disorders, and Unspecified Caffeine-Related Disorders [1]. Caffeine Use Disorder (addiction) is listed as a condition for further study in DSM-5.

Affecting an estimated 7% of the US population, caffeine intoxication is marked by recent use of caffeine, typically in doses in excess of 250 mg, and five or more of the following factors, causing significant distress or impairments in social, occupational, or other important areas of functioning: restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal disturbance, muscle twitching, rambling flow of thought and speech, tachycardia or cardiac arrhythmia, periods of inexhaustibility, and/or psychomotor agitation. Symptoms usually resolve without lasting consequence within 24 hours of onset, consistent with caffeine's 4–6 hour half-life. However, deaths have been reported following extremely high-dose ingestions (5–10 grams) [1].

Frequent ingestion of caffeine can reliably result in the development of physiological tolerance. Development of tolerance is, in part, the result of adenosine A_1 receptor upregulation in chronic caffeine exposure. Abrupt discontinuation or marked reduction in amount consumed of caffeine in a tolerant individual can result in a clinically significant withdrawal syndrome characterized by 24 hours of three or more of the following symptoms causing significant distress and impairments in social, occupational, or other important areas of functioning: headache; marked fatigue or drowsiness; dysphoric mood, depressed mood, or irritability; difficulty concentrating; flu-like symptoms such as nausea, vomiting, or muscle pain/stiffness. Headache is a particularly common symptom, affecting upwards of 50% of those with caffeine withdrawal. Most symptoms resolve within 2–9 days [1].

In part due to the difficulty in defining a caffeine use disorder (addiction), treatment of problematic caffeine use is poorly studied. One study utilized a combination of manualized cognitive behavioral therapy in conjunction with caffeine down-taper over 5 weeks and showed significant caffeine intake reduction that was successfully maintained at the 1-year follow-up timepoint [13].

Tobacco cigarette smokers and alcohol-dependent individuals have been shown to consume significantly higher amounts of caffeine than individuals without these disorders [14] Caffeine has also been shown to have a potentiating effect on other

classical psychostimulants [15]. Furthermore, caffeine has been shown to decrease the metabolism of the atypical antipsychotic clozapine and lithium toxicity has been documented during withdrawal from caffeine related to changes in renal clearance of lithium following discontinuation of caffeine [16, 17].

Caffeine readily crosses the placenta, and meta-analytic data suggest that maternal caffeine consumption during pregnancy has a small but significant association with adverse pregnancy outcomes such as increased rates of spontaneous abortion, stillbirth, low birth weight, and small for gestational age (SGA) in a dose-response pattern [18]. However, the thresholds for risk increase are uncertain and several studies have presented conflicting conclusions about this association [19, 20]. As a result, the American College of Obstetrics and Gynecology, the American Pregnancy Association, and the March of Dimes recommend that pregnant women limit their caffeine intake, generally to 200 mg or less daily [21, 22]. The half-life of caffeine may increase significantly late in pregnancy [23], increasing the risk of toxicity. A small amount of caffeine is found in breastmilk of nursing mothers. The American Academy of Pediatrics indicates that caffeine consumption is safe during breastfeeding, but consumption in excess of two to three cups of coffee per day (300 mg) has been associated with irritability and poor sleeping patterns in nursing infants [24].

Diagnostic Considerations for Cocaine and Other Stimulants

The DSM-5 consolidates the diagnostic criteria for all non-caffeine/tobacco stimulants around 3 categories of substances: (1) amphetamine-type substances, (2) cocaine, and (3) other or unspecified stimulants (e.g., *khât*, cathinone derivatives). DSM-5 diagnoses in relation to stimulants parallel those of caffeine described above: Stimulant Intoxication, Stimulant Withdrawal, Other Stimulant-Induced Disorder, Unspecified Stimulant-Related Disorder, and Stimulant Use Disorder (addiction). For each diagnostic entity, the diagnostic criteria are shared, but the specific stimulant is specified (e.g., Cocaine Use Disorder, Methamphetamine Intoxication, *khât* withdrawal, etc.) [1]. While there are substance-specific considerations, it is efficient and clinically useful to consolidate (as the DSM-5 does) all non-caffeine/tobacco stimulant-related disorders. Therefore, in this section, the broad category of stimulant-related disorders will be outlined, followed by sections specifically highlighting unique considerations for cocaine, amphetamine, and amphetamine-type stimulants, in turn.

The DSM-5 diagnosis of Stimulant Intoxication is marked by clinically significant problematic behavioral or psychological changes such as hallucinations, agitation, euphoria, delusions (e.g., paranoia), and two or more of the following: tachycardia or bradycardia; pupillary dilation; elevated of lowered blood pressure; perspiration or chills; nausea or vomiting; evidence of weight loss; psychomotor agitation or retardation; muscle weakness, respiratory depression, chest pain, or cardiac arrhythmias; confusion, seizures, hyperpyrexia, dyskinesias, dystonias, or coma [1]. Psychomotoric activation and vital sign elevation typically predominate,

with psychomotoric retardation and bradycardia/hypotension seen less frequently and if seen is more likely witnessed in chronic heavy stimulant users.

There are several acute medical complications of stimulant intoxication that are worth specifically highlighting. Stimulants are known to decrease seizure threshold, with case series describing generalized tonic-clonic seizures in individuals with no previously evident seizure disorder [25]. Hyperthermia and trauma resulting from the combination of psychomotoric activation and altered mentation (psychosis and/or delirium) resulting from acute stimulant ingestion can also be life-threatening. Cerebral and cardiac vasoconstriction can be marked with stimulant intoxication and can lead to stroke and myocardial infarction [26]. Pulmonary edema, hemorrhage, pneumothorax, and pneumomediastinum have all been documented with stimulant inhalation and intravenous use. A combination of intramuscular artery vasoconstriction, direct toxic effects of stimulants, and/or muscle damage secondary to seizures or hyperthermia can result in renal damage through ischemia and/or rhabdomyolysis [27]. Gastrointestinal and other organ ischemia are also possible through the potent vasoconstrictive effects of stimulants [27]. Therefore, appropriate medical work-up of the stimulant intoxicated individual is essential to diagnose acute, life-threatening, complications and make sure that they are appropriately managed in a timely fashion.

Psychiatrically, psychosis is common among stimulant-intoxicated individuals and can be profound. Hallucinations may be auditory, visual, or somatosensory (especially tactile hallucinations of bugs crawling under the skin known as fomication). The presence of visual or somatosensory hallucinations is unusual in schizophrenia, which is marked by predominance of auditory hallucinations and negative affective and cognitive symptoms, making this a potentially useful way of distinguishing between these two oft-conflated disease entities. Paranoid delusions are also common in stimulant intoxication, and may contribute to aggressive or violent behavior [28, 29]. Unfortunately, psychotic symptoms may persist long after stimulant intoxication, especially in the use of methamphetamine, in which the psychosis may last for a year or longer after discontinuation [30]. In part related to psychosis generated by stimulant use, an increased risk of violence has been associated with cocaine and AAT intoxication (even between episodes of intoxication [31]), but the association with methamphetamine use, in particular, is well documented [29, 32].

Treatment of stimulant intoxication involves a combination of environmental modifications to ensure safety as well as pharmacologic interventions to treat symptoms. Behavioral interventions are centered on decreasing environmental stimuli and providing calm reassurance and support. Physical restraints are a measure of last resort, since these may contribute to hyperthermia and rhabdomyolysis. Pharmacologically, sedative-hypnotics such as benzodiazepines are preferred, particularly those that are available through oral, intravenous, and intramuscular routes of administration. Diazepam [10–30 mg PO or 2–10 mg IM or IV] or lorazepam [2–4 mg PO or 1–2 mg IM or IV] are commonly used [33]. In the very agitated or psychotic stimulant-intoxicated individual, antipsychotic medications are used with caution. These medications may compound the seizure threshold lowering effects of

stimulants, as well as exacerbate hyperthermia. Therefore, high potency antipsychotics are preferred, such as haloperidol, since these high potency neuroleptics are less likely to have anticholinergic side effects that are particularly implicated in the development of the risks highlighted above.

Prolonged use of stimulants can lead to the development of physiological tolerance, and upon abrupt discontinuation or dose reduction a clinically significant stimulant withdrawal syndrome can develop. Stimulant withdrawal is not typically life-threatening, and manifests characteristically as the opposite of intoxication; namely, a clinically distressing or impairing dysphoric mood and 2+ of the following: fatigue, vivid unpleasant dreams, insomnia or hypersomnia, increased appetite, psychomotor retardation or agitation [1]. Individual variability is significant, but onset of stimulant withdrawal is typically between several hours to days after last use and can last for several days, with some symptoms such as psychosis (see above) persisting even longer.

There are no specific pharmacologic treatments for stimulant withdrawal. Generally, stimulant withdrawal is marked by minimal physiological distress and targeted symptomatic treatment of non-specific musculoskeletal pain, tremors, chills, and other symptoms can be helpful. Psychiatric sequalae of stimulant withdrawal such as disproportionate dysphoria or low-level psychosis can be treated with antidepressants or antipsychotic medications, respectively.

Other Stimulant-Induced Disorders include those disorders that mimic other primary psychiatric disorders but are precipitated by the use of particular substances. In particular, in methamphetamine-induced psychotic disorder, significantly distressing or impairing delusions or hallucinations predominate the clinical presentation and by history, physical exam, or laboratory findings, these symptoms are temporally related to intoxication or withdrawal from methamphetamine use.

There are several approaches to screening for stimulant use and stimulant use disorders. Patient self-report has been demonstrated to be reasonably accurate, so long as there are not competing motivations for misrepresentation of use (e.g., legal ramifications) [34]. Other validated easy-to-use screening tools for stimulant use include the three question Tobacco, Alcohol, Prescription Medication, and Other Substance Use screening instrument [35], the single question screening test [36], and the 10-item Drug Abuse Screening Test [37], while the Screen of Drug Use can be effective in detecting stimulant use disorder [38]. For detection of stimulant use during pregnancy (in addition to other substances and alcohol), the 4Ps Plus is a five-item, validated screen that is easy-to-use [39].

Cocaine

Cocaine is a classical stimulant and analgesic alkaloid chemical that is present in the leaves of the *Erythroxylum* (coca) bush endemic to the higher altitude (1500–6000 feet) regions of the Andes Mountains in South America. For thousands of years, preparations using the coca plant have been used by local populations to stave off altitude sickness and enhance energy and performance in addition to the

treatment of a wide range of physical disorders. Since then, cocaine has developed both medical and non-medical uses. Medically, in the United States, cocaine is a schedule II substance with FDA indication for local and topical analgesia. Historically, cocaine has found particular medical usage as anesthesia for dental, ophthalmologic, and nasal surgical procedures. However, due to the development of other synthetic local anesthetics with more favorable side effect profiles, cocaine is rarely used in modern medical practice. In the latter part of the nineteenth century, cocaine was also added to various consumer products such as alcoholic beverages and soft drinks (e.g., Coca-Cola), a practice which ended in the early 1900s.

Cocaine exerts its psychomotor and reinforcing effects primarily through augmentation of transmission of the catecholamines dopamine and norepinephrine. This is achieved through the blockade of transporters that would otherwise clear previously released catecholamines from the extracellular space. In other words, cocaine acts as a *reuptake* blocker that enables dopamine and norepinephrine to spend greater time in the extracellular space, where they can continue to activate psychostimulatory pathways to a greater extent than would be otherwise naturally possible. In particular, cocaine potently augments dopamine neurotransmission in the mesocorticolimbic pathway involved in reward processing which accounts for its extraordinarily rewarding and reinforcing effect. Secondarily, cocaine also blocks neuronal sodium channels, which accounts for its anesthetic properties.

Cocaine exists in two chemical forms, salt and base, each of which has unique characteristics that drive use patterns. Illicit cocaine is extracted in bulk from the coca leaf, concentrated, purified, and converted chemically into its salt form through acidification. As a salt, cocaine is readily absorbable through mucous membranes making it ideal for intranasal use (insufflation). The salt is also readily dissolvable in water making it thereby available for injection. However, cocaine salt has a high melting point which provides little margin between the vaporization point and "burning" point of the chemical. Since burning cocaine renders it pharmacologically useless, cocaine salt is therefore not ideal for vaporized inhalation. However, converting the cocaine salt into its base form through alkalization drops the melting point significantly and allows for vaporization that facilitates easy ingestion through inhalation. The base form, conversely, is poorly dissolvable making it less ideal for injection and insufflated administration. The so-called "freebase" cocaine results in what has been commonly known as "crack," the use of which reached epidemic proportions in the 1980s. While it is often referred to as being "smoked," technically freebase cocaine is vaporized, not burned, unlike other smoked substances such as tobacco.

Ingested orally the onset of effect is relatively slower (30–45 minutes) than via insufflation (1–5 minutes) intravenous (4–7 minutes) or vaporized inhalation (6–8 seconds) routes of administration, with times to peak effect being 60–90 minutes, 20–30 minutes, 3-5 minutes, and 3–5 minutes, respectively. Correspondingly, the duration of action is longer for cocaine ingested orally (3 hours), via insufflation (1 hour), than via intravenous or inhalation (15–30 minutes) routes of administration [40]. When consumed with alcohol a new compound, cocaethylene, is formed with less potency than cocaine but with a longer half-life, as well as the potential to cause cardiac arrhythmias [41].

Cocaine is primarily metabolized via ester bond hydrolysis in the liver to benzoylecgonine which is readily detectable via routine immunoassay in urine for 2–3 days in non-daily users, but upwards of 2 weeks in those who use cocaine heavily.[1] Cocaine may also be detected through hair, blood, sweat (via patches), and oral fluid samples, with varying times of positivity (up to 12 hours in blood and oral fluids, weeks for sweat, to months-years in hair, although hair testing results may vary significantly based on race/ethnicity, location of hair sample, and the presence of hair treatments) [42].

While a urine assay positive for benzoylecgonine is reliably indicative of cocaine use, test positivity does not, in-and-of itself, indicate the presence of a cocaine use disorder (addiction). Rather, cocaine use disorder is diagnosed through screening for the range of behavioral and physical criteria described in the DSM-5 for all other substance use disorders (described elsewhere in this text).

In 2017, 20%, 3%, and 1% of US residents 18 years and older reported use of cocaine in their lifetime, in the past year, and in the past month, respectively. The predominance of past year users are white or American Indian or Alaska Native unemployed men with some college education [43]. Most cocaine users use relatively infrequently (58% report using only 12 times a year), in what is typically described as a "binge" involving long periods of little or no use punctuated by short periods of heavy use. Cocaine users frequently describe symptoms of depression and anxiety, and are likely to use other substances (in particular tobacco and alcohol) to mediate or enhance the effects of intoxication or withdrawal [44].

In addition to the medical and psychiatric sequelae discussed above for stimulants in general, cocaine use is associated with several specific consequences, acute and chronic: cognitive impairment [45], suicidality and suicide attempts [46], and increased risk of infections such as hepatitis and HIV (by any route of administration) [47]. Insufflated cocaine can cause perforation of the nasal septum, while cocaine use via any route of administration can cause acute and chronic movement disorders such as choreoathetosis, dystonia (especially in conjunction with neuroleptic medications), and akathisia [48]. Vaporized cocaine is also associated with a severe pulmonary syndrome characterized by fever, hypoxemia, hemoptysis, respiratory failure, and eosinophilic alveolar infiltrates—the so-called "crack lung." [49]

Cocaine ingestion in pregnancy has been associated with several deleterious consequences (either as a direct result of cocaine use, or due to other environmental factors associated with its use), including: vaginal bleeding, abruptio placenta, placenta previa, premature rupture of membranes, premature birth, decreased head circumference, low birth weight, and autonomic instability [50]. In addition, cocaine is found in breastmilk and infants breastfed from mothers using cocaine may demonstrate irritability, sleep difficulty, and tremors [24].

[1] Windows of detection are dependent on a number of factors, including the relative cut-off levels of the individual tests. For example, a test with a lower cut-off level could potentially detect both a smaller amount of substance used as well as detect the presence of a substance for a longer period of time following exposure.

For the treatment of cocaine use disorders, randomized trials have examined the roles of novel cocaine vaccines, as well as stimulant replacement medication strategies, dopamine agonists, various antidepressants (e.g., fluoxetine, desipramine, bupropion), GABAergic medications (e.g., topiramate, vigabatrin), cholinergic medications (e.g., galantamine), ondansetron, and disulfiram. None of these pharmacotherapies have demonstrated consistent efficacy in treating cocaine use disorder.

Relative to pharmacotherapeutic interventions, behavioral treatment strategies have met with greater success in the treatment of cocaine use disorders [51]. Behavioral therapies represent a wide array of interventions that target various aspects of the challenges inherent in addictive disorders, from helping to explore and resolve ambivalence around usage (motivational interviewing (MI), motivational enhancement therapy(MET)), enhancing coping strategies (cognitive behavioral therapy (CBT)), altering thought processes around use (cognitive therapy (CT), CBT), learning how to utilize techniques to avoid/prevent triggers (CBT), changing the environmental reinforcing contingencies (contingency management (CM), community reinforcement approach (CRA)), to promoting a sense of detachment from cravings, thoughts, and emotions that contribute to relapse (mindfulness/meditation therapies). A 2008 meta-analysis of psychosocial/behavioral treatments for multiple substance use disorders showed medium to large effect sizes in impacting cocaine use ($d = 0.62$) [52]. In addition to the treatment interventions included in the meta-analysis above, additional studies have demonstrated the effectiveness of MI/MET [53], especially when coupled with CBT treatment [54]. Mindfulness-based treatments such as Acceptance and Commitment Therapy (ACT), Dialectical Behavioral Therapy (DBT), Mindfulness-Based Stress Reduction (MBSR), and Transcendental Meditation (TM) are used widely in substance use treatment, but the data evaluating these in individuals using cocaine are limited [56].

Twelve-step fellowships (e.g., alcoholics anonymous, narcotics anonymous, cocaine anonymous) are ubiquitously available abstinence-based substance use treatment programming, often employed alone or in tandem with other treatment approaches, and have been shown to be helpful for some with cocaine use, especially those who actively participate in the fellowship programming [55].

Amphetamine and Amphetamine-Type Stimulants

Amphetamine and amphetamine-type (AAT) stimulants are a diverse array of compounds (amphetamine, methamphetamine, dextroamphetamine) that are either structurally related to a parent phenethylamine chemical compound, or have similar effects but are structurally unrelated (methylphenidate, *Ephedra*, *cathinone*). Unlike cocaine, AAT stimulants continue to be widely used in medical practice for the treatment of a wide array of FDA-approved indications, making them readily available through licit supply chains. Diversion of AAT stimulants from these licit sources, in combination with a robust illicit manufacture and supply chain, contributes to their widespread availability. National surveys indicate that non-medical use

of stimulants has been increasing, with 2014 surveys highlighting that 0.6% of the population ages 12 or older reports current nonmedical use of stimulants (0.2% methamphetamine, specifically), which represents an increase over most years between 2005 and 2013 [56].

Ephedrine-containing *Ephedra* plants have been used in Chinese medicine for thousands of years, and continued to be used widely in weight loss products until being banned from the US market in 2006 due to ephedrine's association with serious cardiac side effects. α-methylphenethylamine (amphetamine) was first synthesized in 1887 but lay fallow until 1927 when G.A. Alles brought the chemical to mainstream medicine while he was seeking a synthetic substitute for ephedrine [57]. Methamphetamine was first synthesized from ephedrine in Japan in 1897, but found significant widespread use during World War II where it was broadly distributed by German military leadership to enhance wakefulness and combat performance.

Amphetamine exists in two optically active isomers, dextro (or *d*-) and levo- (or *l*-), with the d-isomer (trade name, Dexedrine) being significantly more potent. Similar to amphetamine, methamphetamine exists in two isomers (*l*- and *d*-) with *d*-methamphetamine being a highly potent stimulant, while *l*-methamphetamine has virtually no intrinsic psychoactivity. Both *l*- and *d*-amphetamine and *d*-methamphetamine are Schedule II medications in the United States (indicative of their high abuse potential), while *l*-methamphetamine is available over the counter as a decongestant nasal spray.

Methamphetamine exists in both base and salt forms, with the former being liquid at room temperature and the latter being a clear crystal at room temperature (e.g., "crystal methamphetamine"). The crystalline form of methamphetamine is readily dissolved in water and injected, or vaporized and inhaled in a manner similar to crack cocaine. Anecdotally, methamphetamine is felt to be a more potent and dangerous psychostimulant than amphetamine; however, rat and human studies have not consistently supported this assertion [58]. However, it is conceivable that these anecdotal differences are based on actual chemical differences. For example, methamphetamine is more lipophilic than amphetamine and therefore more readily crosses the blood–brain barrier leading to more rapid onset of action which can have potent reinforcing effects. Additionally, methamphetamine may be more resistant to enzymatic degradation, thereby enhancing its effect through prolongation of action ($t_{1/2}$ upwards of 30 hours) [59].

Like cocaine, AAT are ingested through several routes of administration, and the clinical presentations of use disorder, intoxication, and withdrawal are all similar to those of cocaine. Some significant differences are worth noting. Some AAT, such as methamphetamine have a significantly longer duration of action (as above, $t_{1/2}$ upwards of 30 hours) relative to cocaine's relatively short duration of action ($t_{1/2}$ around 1.5 hours) [60]. In addition, chronic use of methamphetamine is particularly correlated with significant xerostomia which can lead to noteworthy dental pathology (e.g., "meth mouth"). Chronic AAT use is also tied to significant cognitive deficits and long-lasting psychotic symptoms, both of which are attributable to amphetamine's different mechanism of action (see below) relative to cocaine.

Methamphetamine is metabolized into amphetamine which is then further metabolized via three different metabolic pathways in the liver, unlike cocaine's primary hepatic hydrolytic metabolic pathway. Amphetamine is readily detectable in urine, hair, sweat, blood, and oral fluids. As above, detection windows are dependent on a number of factors, but generally amphetamines are detectable in urine and oral fluids for 2–4 days post-exposure, and up to 90 days in hair. The detection window for amphetamines in blood may be only several hours, depending on amount taken. False-positive test results have been documented on amphetamine immunoassays, especially in individuals also taking buproprion, certain tricyclic antidepressant medications, quetiapine, *l*-methamphetamine nasal inhalers, or ephedrine/pseudoephedrine containing cold medications. Confirmatory testing via gas or liquid chromatography can provide definitive results when false positives may be suspected [31].

While cocaine exerts its pharmacological effect by blocking reuptake of catecholamines, AAT (particularly *d*-amphetamine and *d*-methamphetamine) both block reuptake *and* stimulate direct release of catecholamines. Both amphetamine and *d*-methamphetamine achieve this added pharmacologic effect on catecholaminergic neurons by a complex pathway that involves (1) co-transportation alongside sodium ions into the neuronal cytoplasm, (2) disruption of monoamine vesicular storage causing an intracellular release of catecholamine stores, and (3) increased release of synaptic catecholamines resulting from the increased intracellular availability of these chemicals. Therefore, amphetamine and *d*-methamphetamine are referred to as "transporter substrates," [61] that, in sum, result in relatively higher synaptic release of catecholamines than cocaine. This substantial synaptic and intracellular catecholamine release may have neuronal toxic effects, which has been tied to the prolonged psychosis and significant cognitive impairments that are associated with chronic amphetamine and *d*-methamphetamine use [45]. In addition, chronic use of amphetamine and *d*-methamphetamine has been tied to decreased brain serotonin receptor density, which, in animal models has been associated with increased aggression or violence [62]. Other AATs, however, such as methylphenidate, function pharmacologically more similarly to cocaine (reuptake blockade), whereas *khât* (cathinone) and its synthetic derivatives (e.g., mephedrone) possess catecholamine transporter substrate and reuptake blockade activity (particularly dopamine) and also enhance synaptic serotonin release [63, 64]. Together, these findings highlight the vast diversity of compounds and their respective mechanisms of action that make up this class of drugs.

AAT use during pregnancy can present a complex set of considerations. For example, prescription psychostimulants (amphetamine, methylphenidate) can cross the placental barrier, but used *as directed* have not been shown to have clinically significant associations with preeclampsia, placental abruption, small-for-gestational age neonates, and preterm delivery, despite concerns about vasoconstrictive effects of these medications on placental circulation [65]. On the other hand, pregnant users of illicit methamphetamine have been shown to have greater risks of preeclampsia and gestational hypertension, fetal demise, abortion, and preterm labor [66, 67]. When taken as prescribed, methylphenidate and amphetamine levels

in breastmilk are very low and risk-benefit of continued use should be discussed carefully with nursing women. While some guidelines indicate that use of prescribed psychostimulants during breastfeeding is acceptable, others do not [68].

Similar to the situation with cocaine use disorder, studies of various pharmacotherapies for the treatment of amphetamine and methamphetamine use disorders have not shown significant efficacy, such as prescription psychostimulants, tricyclic antidepressants, SSRIs, ondansetron, topiramate, and amlodipine [69]. However, a small controlled trial of mirtazapine showed significant reductions in methamphetamine use [70], as has risperidone [71], while naltrexone has shown some effect on amphetamine use but not methamphetamine [72].

Behavioral/psychosocial therapies for the treatment of AAT stimulant use disorders span the same gamut as those described above for cocaine. Of those outlined above for cocaine use disorder, however, those with supportive evidence specifically in the treatment of AAT include CBT and contingency management [73]. For some patients, the structure and programmatic organization of an intensive outpatient therapy program for stimulant use disorder may be beneficial. One way of systematically operationalizing these varied treatment approaches has been through use of the manualized Matrix Model, which incorporates educational materials on the effects of stimulant use, family education, 12-Step program participation, and positive reinforcement for behavior change and treatment compliance [74].

Review Questions

1. A 29-year-old male medical resident is studying for his licensing examination. To help stay awake, he has been consuming caffeine-containing "energy" drinks on a nightly basis. The wakefulness-enhancing effects experienced by this resident from caffeine are attributable to its _____ of central _____ receptors, a system which is implicated in the experience of escalating sleepiness during periods of prolonged wakefulness.
   A. Agonism, dopamine
   B. Antagonism, adenosine
   C. Agonism, adenosine
   D. Antagonism, dopamine
   E. Partial agonism, mu-opioid

   Answer: B.

   Explanation: Endogenous adenosine agonizes central A_1 and A_{2A} adenosine receptors, which leads to the experience of increased sleepiness. Caffeine's psychomotor-reinforcing effects and hyperarousal are the result of the antagonism of central A_1 and A_{2A} adenosine receptors.
2. A 37-year-old female intravenous heroin and cocaine user has entered treatment at an opioid treatment program. With initiation of methadone maintenance, the patient achieved abstinence from use of heroin, but she continues to struggle

with cocaine use. To address this, the opioid treatment program enrolls the patient in a program that provides specific reinforcements and sanctions for providing toxicology screens that are negative or positive, respectively, for cocaine. This behavioral strategy of providing environmental reinforcements has been shown to be effective in the treatment of cocaine use disorder, and is known as:

A. Cognitive behavioral therapy
B. Motivational enhancement therapy
C. Acceptance and commitment therapy
D. Contingency management
E. Mindfulness-based stress reduction

Answer: D.

Explanation: Contingency management is an evidence-based behavioral therapy that has been shown to be effective in the treatment of various stimulant use disorders, but cocaine use disorder in particular. In this treatment, individuals are given the opportunity to receive behavioral incentives such as gift cards in the event that they adhere to some predetermined and agreed upon desirable behavior (e.g., attendance at counseling sessions, providing a negative toxicology screen). Correspondingly, individuals receive sanctions (e.g., no gift card, reduction in number of take-home methadone doses provided) should they not adhere to the predetermined and agreed upon desirable behavior.

3. A 35-year-old male who has a history of using illicit opioids has achieved 2 years abstinence from opioids while on buprenorphine-naloxone sublingual therapy. He's at a party where a friend offers him methamphetamine, which he has never used before. Afterwards, he reports to his counselor that the experience of methamphetamine was more rewarding than any other substance he's ever taken, including cocaine. One pharmacological explanation for why methamphetamine was even more reinforcing than cocaine in this individual is:

A. Methamphetamine potently stimulates serotonin receptors, whereas cocaine does not.
B. Methamphetamine blocks the effects of the most widespread inhibitory neurotransmitter in the brain, gamma-aminobutyric acid (GABA), leading to a potent stimulatory effect.
C. Cocaine's ability to block neuronal sodium channels lessens its pleasurable effect relative to methamphetamine which has no effect on neuronal sodium channels.
D. Methamphetamine not only blocks reuptake of dopamine in the synapse, but also causes vesicular release of dopamine into the synaptic cleft. This results in a surge in dopamine that accounts for methamphetamine's intensely rewarding experience relative to most other drugs of abuse.
E. The patient must have also used a sedative medication or alcohol with the methamphetamine in order to produce an intensely pleasurable "speedball" effect, since methamphetamine alone is not very reinforcing or rewarding.

Answer: D.

Explanation: Much of cocaine's psychostimulatory effects are mediated through its ability to increase synaptic dopamine levels by inhibiting dopamine reuptake. By contrast, methamphetamine (and amphetamine) produce their psychostimulatory effects by both blocking dopamine (and other catecholamine) reuptake, as well as disrupting monoamine vesicular storage causing an intracellular release of catecholamine stores with consequent increased release of synaptic catecholamines.

4. A 46-year-old female methamphetamine user is talking with her physician at a residential treatment program. She says to her physician: "I've heard of people with heroin addiction taking methadone or buprenorphine to treat their heroin addiction. I want to learn more about medications to treatment my methamphetamine addiction." Her addiction medicine-boarded physician most accurately responds:
   A. "That's fantastic. There is a great new option of a methamphetamine vaccine that just got approved for use in the U.S."
   B. "Methadone and buprenorphine are just replacing one addiction for another, so I would not recommend thinking about any medications for your addiction, or any addiction for that matter."
   C. "Researchers have tried many different kinds of medications to treat methamphetamine use disorder, and unfortunately none of them have shown a strong enough positive effect to warrant widespread use."
   D. "I'll get you started today with a prescription for amphetamine that you can take instead of taking methamphetamine."
   E. "Several large-scale studies have demonstrated that topiramate is effective in treating methamphetamine addiction. I recommend that we start that today."

   Answer: C.

   Explanation: Small studies have demonstrated some possible effect of mirtazapine and risperidone on the use of methamphetamine. However, larger studies have not demonstrated large enough beneficial effects for any medication in the treatment of methamphetamine use disorder to warrant widespread use in treatment.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Association; 2013.
2. Anthony JC, Warner LA, Kessler RD. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey. Exp Clin Psychopharmacol. 1994;2:244–68.
3. Woody GE, Cttler LB, Cacciola J. Severity of dependence: data from the DSM-IV field trials. Addiction. 1993;88(1):1573–9.
4. Compton WM, Volkow ND. Abuse of prescription drugs and the risk of addiction. Drug and Alcohol Dependence. 2006;83(supplement 1):S4–S7.
5. Fischer TW, Hipler UC, Elsner P. Effect of caffeine and testosterone on the proliferation of human hair follicles in vitro. Int J Dermatol. 2007;46(1):27–35. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-4632.2007.03119.x. https://doi.org/10.1111/j.1365-4632.2007.03119.x.

6. Mitchell DC, Knight CA, Hockenberry J, Teplansky R, Hartman TJ. Beverage caffeine intakes in the U.S. Food Chem Toxicol. 2014;63:136–42. https://www.sciencedirect.com/science/article/pii/S0278691513007175. https://doi.org/10.1016/j.fct.2013.10.042.
7. Saab S, Mallam D, Cox GA, Tong MJ. Impact of coffee on liver diseases: a systematic review. Liver Int. 2014;34(4):495–504. https://onlinelibrary.wiley.com/doi/abs/10.1111/liv.12304. https://doi.org/10.1111/liv.12304.
8. Grosso G, Micek A, Castellano S, Pajak A, Galvano F. Coffee, tea, caffeine and risk of depression: a systematic review and dose–response meta-analysis of observational studies. Mol Nutr Food Res. 2016;60(1):223–34. https://onlinelibrary.wiley.com/doi/abs/10.1002/mnfr.201500620. https://doi.org/10.1002/mnfr.201500620.
9. Carman AJ, Dacks PA, Lane RF, Shineman DW, Fillit HM. Current evidence for the use of coffee and caffeine to prevent age-related cognitive decline and alzheimer's disease. J Nutr Health Aging. 2014;18(4):383. https://www.ncbi.nlm.nih.gov/pubmed/24676319. https://doi.org/10.1007/s12603-014-0021-7.
10. Derry CJ, Derry S, Moore RA. Caffeine as an analgesic adjuvant for acute pain in adults. Cochrane Database Syst Rev. 2014;12:CD009281. https://www.ncbi.nlm.nih.gov/pubmed/25502052. https://doi.org/10.1002/14651858.CD009281.pub3.
11. Schmidt B, Roberts RS, Davis P, et al. Caffeine therapy for apnea of prematurity. N Engl J Med. 2006;354(20):2112–21. http://content.nejm.org/cgi/content/abstract/354/20/2112. https://doi.org/10.1056/NEJMoa054065.
12. James JE. Critical review of dietary caffeine and blood pressure: a relationship that should be taken more seriously. Psychosom Med. 2004;66(1):63–71.
13. Evatt DP, Juliano LM, Griffiths RR. A brief manualized treatment for problematic caffeine use: a randomized control trial. J Consult Clin Psychol. 2016;84(2):113–21. https://www.ncbi.nlm.nih.gov/pubmed/26501499. https://doi.org/10.1037/ccp0000064.
14. Strain EC, Mumford GK, Silverman K, Griffiths RR. Caffeine dependence syndrome: evidence from case histories and experimental evaluations. JAMA. 1994;272(13):1043–8. https://doi.org/10.1001/jama.1994.03520130081037.
15. Oliveto AH, McCance-Katz E, Singha A, Hameedi F, Kosten TR. Effects of d-amphetamine and caffeine in humans under a cocaine discrimination procedure. Behav Pharmacol. 1998;9(3):207. https://www.ncbi.nlm.nih.gov/pubmed/9832935
16. Carrillo JA, Benitez J. Clinically significant pharmacokinetic interactions between dietary caffeine and medications. Clin Pharmacokinet. 2000;39(2):127–53.
17. Hagg S, Spigset O, Mjorndal T, Dahlqvist R. Effect of caffeine on clozapine pharmacokinetics in healthy volunteers. Br J Clin Pharmacol. 2000;49(1):59–63. http://www.ingentaconnect.com/content/bsc/bjcp/2000/00000049/00000001/art00008. https://doi.org/10.1046/j.1365-2125.2000.00111.x.
18. Greenwood DC, Thatcher NJ, Ye J, et al. Caffeine intake during pregnancy and adverse birth outcomes: a systematic review and dose-response meta-analysis. Eur J Epidemiol. 2014;29(10):725–34. https://www.jstor.org/stable/43775025. https://doi.org/10.1007/s10654-014-9944-x.
19. Savitz DA, Chan RL, Herring AH, Howards PP, Hartmann KE. Caffeine and miscarriage risk. Epidemiology. 2008;19(1):55–62. https://www.jstor.org/stable/20486494. https://doi.org/10.1097/EDE.0b013e31815c09b9.
20. Weng X, Odouli R, Li D-K. Maternal caffeine consumption during pregnancy and the risk of miscarriage: a prospective cohort study. Am J Obstet Gynecol. 2008;198(3):279.e8. https://www.clinicalkey.es/playcontent/1-s2.0-S000293780702025X. https://doi.org/10.1016/j.ajog.2007.10.803.
21. Caffeine intake during pregnancy. Americanpregnancy.org Web site. http://americanpregnancy.org/pregnancy-health/caffeine-intake-during-pregnancy/. Updated 2018. Accessed 9 February, 2019.
22. ACOG CommitteeOpinion no. 462: moderate caffeine consumption during pregnancy. Obstet Gynecol. 2010;116(2 Pt 1):467. https://www.ncbi.nlm.nih.gov/pubmed/20664420
23. Aldridge A, Bailey J, Neims AH. The disposition of caffeine during and after pregnancy. Semin Perinatol. 1981;5(4):310. https://www.ncbi.nlm.nih.gov/pubmed/7302604

24. Committee on Drugs. The transfer of drugs and other chemicals into human milk. Pediatrics. 2001;108(3):776–89. http://pediatrics.aappublications.org/cgi/content/abstract/108/3/776. https://doi.org/10.1542/peds.108.3.776.
25. Brust JC. Neurologic complications of illicit drug abuse. Continuum (Minneap Minn). 2014;20(3, Neurology of Systemic Disease):642–56. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=n&CSC=Y&PAGE=fulltext&D=ovft&AN=00132979-201406000-00016. https://doi.org/10.1212/01.CON.0000450971.99322.cd.
26. Sordo L, Indave BI, Barrio G, Degenhardt L, de la Fuente L, Bravo MJ. Cocaine use and risk of stroke: a systematic review. Drug Alcohol Depend. 2014;142:1–13. https://www.clinicalkey.es/playcontent/1-s2.0-S0376871614009685. https://doi.org/10.1016/j.drugalcdep.2014.06.041.
27. Glauser J, Queen JR. An overview of non-cardiac cocaine toxicity. J Emerg Med. 2007;32(2):181–6. https://www.clinicalkey.es/playcontent/1-s2.0-S073646790600655X. https://doi.org/10.1016/j.jemermed.2006.05.044.
28. Brecht M, Herbeck DM. Methamphetamine use and violent behavior. J Drug Issues. 2013;43(4):468–82. https://journals.sagepub.com/doi/full/10.1177/0022042613491098. https://doi.org/10.1177/0022042613491098.
29. McKetin R, Lubman DI, Najman JM, Dawe S, Butterworth P, Baker AL. Does methamphetamine use increase violent behaviour? Evidence from a prospective longitudinal study. Addiction. 2014;109(5):798–806. https://onlinelibrary.wiley.com/doi/abs/10.1111/add.12474. https://doi.org/10.1111/add.12474.
30. Glasner-Edwards S, Mooney L. Methamphetamine psychosis: epidemiology and management. CNS Drugs. 2014;28(12):1115–26. https://www.ncbi.nlm.nih.gov/pubmed/25373627. https://doi.org/10.1007/s40263-014-0209-8.
31. Gerra G, Zaimovic A, Ampollini R, et al. Experimentally induced aggressive behavior in subjects with 3,4-methylenedioxy-methamphetamine ("ecstasy") use history: psychobiological correlates. J Subst Abus. 2001;13(4):471–91. https://www.ncbi.nlm.nih.gov/pubmed/11775077
32. Tyner, Elizabeth A.|Fremouw, William J. The relation of methamphetamine use and violence: a critical review. Aggress Violent Behav 2008;13(4):285–297. https://www.clinicalkey.es/playcontent/1-s2.0-S1359178908000189. https://doi.org/10.1016/j.avb.2008.04.005.
33. Srisurapanont M, Kittiratanapaiboon P, Jarusuraisin N. Treatment for amphetamine psychosis. Cochrane Database Syst Rev. 2001;4:CD003026. https://www.ncbi.nlm.nih.gov/pubmed/11687172
34. Hjorthøj CR, Hjorthøj AR, Nordentoft M. Validity of timeline follow-back for self-reported use of cannabis and other illicit substances — systematic review and meta-analysis. Addict Behav. 2011;37(3):225–33. https://www.clinicalkey.es/playcontent/1-s2.0-S030646031100387X. https://doi.org/10.1016/j.addbeh.2011.11.025.
35. McNeely J, Wu L, Subramaniam G, et al. Performance of the tobacco, alcohol, prescription medication, and other substance use (TAPS) tool for substance use screening in primary care patients. Ann Intern Med. 2016;165(10):690. https://www.ncbi.nlm.nih.gov/pubmed/27595276. https://doi.org/10.7326/M16-0317.
36. Smith PC, Schmidt SM, Allensworth-Davies D, Saitz R. A single-question screening test for drug use in primary care. Arch Intern Med. 2010;170(13):1155. https://doi.org/10.1001/archinternmed.2010.140.
37. Skinner HA. The drug abuse screening test. Addict Behav. 1982;7(4):363.
38. Tiet QQ, Leyva YE, Moos RH, Frayne SM, Osterberg L, Smith B. Screen of drug use: diagnostic accuracy of a new brief tool for primary care. JAMA Intern Med. 2015;175(8):1371–7. https://doi.org/10.1001/jamainternmed.2015.2438.
39. Chasnoff IJ, Wells AM, McGourty RF, Bailey LK. Validation of the 4Ps plus screen for substance use in pregnancy validation of the 4Ps plus. J Perinatol. 2007;27(12):744–8. https://www.ncbi.nlm.nih.gov/pubmed/17805340. https://doi.org/10.1038/sj.jp.7211823.
40. Jenkins AJ, Cone EJ. Pharmacokinetics: drug absorption, distribution, and elimination. In: Karch SB, editor. Drug abuse handbook. Boca Raton: CRC Press; 1998.

41. Pennings EJM, Leccese AP, Wolff FA. Effects of concurrent use of alcohol and cocaine. Addiction. 2002;97(7):773–83. http://www.ingentaconnect.com/content/bsc/add/2002/00000097/00000007/art00002. https://doi.org/10.1046/j.1360-0443.2002.00158.x.
42. Verstraete AG. Detection times of drugs of abuse in blood, urine, and oral fluid. Ther Drug Monit. 2004;26(2):200–5. https://www.ncbi.nlm.nih.gov/pubmed/15228165. https://doi.org/10.1097/00007691-200404000-00020.
43. Center for behavioral health statistics and quality. 2017 national survey on drug use and health: detailed tables. Substance Abuse and Mental Health Services Administration. 2018.
44. Results from the 2013 national survey on drug use and health: summary of national findings, NSDUH series H-48, HHS publication no. (SMA) 14-4863. Office of Applied Studies, Substance Abuse and Mental Health Services Administration. 2014.
45. Rogers RD, Robbins TW. Investigating the neurocognitive deficits associated with chronic drug misuse. Curr Opin Neurobiol. 2001;11(2):250–7.
46. Marzuk PM, Tardiff K, Leon AC, Stajic M, Morgan EB, Mann JJ. Prevalence of cocaine use among residents of New York city who committed suicide during a one-year period. Am J Psychiatr. 1992;149(3):371–5. https://doi.org/10.1176/ajp.149.3.371.
47. Friedman H, Pross S, Klein TW. Addictive drugs and their relationship with infectious diseases. FEMS Immunol Med Microbiol. 2006;47(3):330–42. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1574-695X.2006.00097.x. https://doi.org/10.1111/j.1574-695X.2006.00097.x.
48. van Harten PN, van Trier JC, Horwitz EH, Matroos GE, Hoek HW. Cocaine as a risk factor for neuroleptic-induced acute dystonia. J Clin Psychiatry. 1998;59(3):128–30. https://www.ncbi.nlm.nih.gov/pubmed/9541156. https://doi.org/10.4088/JCP.v59n0307.
49. Tseng W, Sutter M, Albertson T. Stimulants and the lung. Clinic Rev Allerg Immunol. 2014;46(1):82–100. https://www.ncbi.nlm.nih.gov/pubmed/23760760. https://doi.org/10.1007/s12016-013-8376-9.
50. Kuczkowski KM. The effects of drug abuse on pregnancy. Curr Opin Obstet Gynecol. 2007;19(6):578–85.
51. Penberthy JK, Ait-Daoud N, Vaughan M, Fanning T. Review of treatment for cocaine dependence. Curr Drug Abuse Rev. 2010;3(1):49. https://www.ncbi.nlm.nih.gov/pubmed/20088819
52. Otto MW, Leyro TM, Powers MB, Dutra L, Basden SL, Stathopoulou G. A meta-analytic review of psychosocial interventions for substance use disorders. Am J Psychiatr. 2008;165(2):179–87. https://doi.org/10.1176/appi.ajp.2007.06111851.
53. Stotts AL, Schmitz JM, Rhoades HM, Grabowski J. Motivational interviewing with cocaine-dependent patients. J Consult Clin Psychol. 2001;69(5):858–62. https://www.ncbi.nlm.nih.gov/pubmed/11680565. https://doi.org/10.1037/0022-006X.69.5.858.
54. McKee SA, Carroll KM, Sinha R, Robinson JE, Nich C, Cavallo D, O'Malley S. Enhancing brief cognitive-behavioral therapy with motivational enhancement techniques in cocaine users. Drug Alcohol Depend. 2007;91(1):97–101. https://www.clinicalkey.es/playcontent/1-s2.0-S0376871607001949. https://doi.org/10.1016/j.drugalcdep.2007.05.006.
55. Hatch-Maillette M, Wells EA, Doyle SR, Brigham GS, Daley D, DiCenzo J, Donovan D, Garrett S, Horigian VE, Jenkins L, Killeen T, Owens M, Perl HI. Predictors of 12-step attendance and participation for individuals with stimulant use disorders. J Subst Abuse Treat. 2016;68:74–82. https://www.clinicalkey.es/playcontent/1-s2.0-S0740547216300125. https://doi.org/10.1016/j.jsat.2016.06.007.
56. Hedden SL, Kennet J, Lipari R, Medley G, Tice P. Center for behavioral health statistics and quality. Behavioral health trends in the United States: results from the 2014 national survey on drug use and health. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. 2015.
57. Heal DJ, Smith SL, Gosden J, Nutt DJ. Amphetamine, past and present – a pharmacological and clinical perspective. J Psychopharmacol. 2013;27(6):479–96. https://journals.sagepub.com/doi/full/10.1177/0269881113482532. https://doi.org/10.1177/0269881113482532.
58. Kirkpatrick MG, Gunderson EW, Johanson C, Levin FR, Foltin RW, Hart CL. Comparison of intranasal methamphetamine and d-amphetamine self-administration by humans.

Addiction. 2012;107(4):783–91. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1360-0443.2011.03706.x. https://doi.org/10.1111/j.1360-0443.2011.03706.x.
59. Schep LJ, Slaughter RJ, Beasley DMG. The clinical toxicology of metamfetamine. Clin Toxicol. 2010;48(7):675–94. https://www.ncbi.nlm.nih.gov/pubmed/20849327. https://doi.org/10.3109/15563650.2010.516752.
60. Baselt RC. Disposition of toxic drugs and chemicals in man. 7th ed. Chemical Toxicology Institute: Foster City; 2004.
61. Sitte HH, Freissmuth M. Amphetamines, new psychoactive drugs and the monoamine transporter cycle. Trends Pharmacol Sci. 2014;36(1):41–50. https://www.clinicalkey.es/playcontent/1-s2.0-S0165614714002120. https://doi.org/10.1016/j.tips.2014.11.006.
62. Sekine Y, Ouchi Y, Takei N, et al. Brain serotonin transporter density and aggression in abstinent methamphetamine abusers. Arch Gen Psychiatry. 2006;63(1):90–100. https://doi.org/10.1001/archpsyc.63.1.90.
63. Baumann MH, Ayestas J, Mario A, Partilla JS, et al. The designer methcathinone analogs, mephedrone and methylone, are substrates for monoamine transporters in brain tissue. Neuropsychopharmacology. 2012;37(5):1192–203. https://www.ncbi.nlm.nih.gov/pubmed/22169943. https://doi.org/10.1038/npp.2011.304.
64. Papaseit E, Moltó J, Muga R, Torrens M, de la Torre R, Farré M. Clinical pharmacology of the synthetic cathinone mephedrone. Curr Top Behav Neurosci. 2017;32:313–31. https://www.ncbi.nlm.nih.gov/pubmed/28012094. https://doi.org/10.1007/7854_2016_61.
65. Cohen J, Hernández-Díaz S, Bateman B, et al. Placental complications associated with psychostimulant use in pregnancy. Obstet Gynecol. 2017;130(6):1192–201. https://www.ncbi.nlm.nih.gov/pubmed/29112657. https://doi.org/10.1097/AOG.0000000000002362.
66. Committee opinion no. 479: methamphetamine abuse in women of reproductive age. Obstetrics and gynecology. 2011;117(3):751–5. https://www.ncbi.nlm.nih.gov/pubmed/21343793. https://doi.org/10.1097/AOG.0b013e318214784e.
67. Dinger J, Hinner P, Reichert J, Rüdiger M. Methamphetamine consumption during pregnancy – effects on child health. Pharmacopsychiatry. 2017;50(3):107–13. https://doi.org/10.1055/s-0042-122711.
68. Ornoy A. Pharmacological treatment of attention deficit hyperactivity disorder during pregnancy and lactation. Pharm Res. 2018;35(3):1–11. https://search.proquest.com/docview/1994705020. https://doi.org/10.1007/s11095-017-2323-z.
69. Gorelick DA. Pharmacological treatment of stimulant use disorders. In: Miller S, Fiellin D, Rosenthal R, Saitz R, editors. The ASAM principles of addiction medicine. 6th ed. Philadelphia: Wolters Kluwer; 2019. p. 847–62.
70. Colfax GN, Santos G, Das M, et al. Mirtazapine to reduce methamphetamine use: a randomized controlled trial. Arch Gen Psychiatry. 2011;68(11):1168–75. https://doi.org/10.1001/archgenpsychiatry.2011.124.
71. Meredith CW, Jaffe C, Yanasak E, Cherrier M, Saxon AJ. An open-label pilot study of risperidone in the treatment of methamphetamine dependence. J Psychoactive Drugs. 2007;39(2):167–72. http://www.tandfonline.com/doi/abs/10.1080/02791072.2007.10399875. https://doi.org/10.1080/02791072.2007.10399875.
72. Beck O, Hammarberg A, Franck J, Jayaram-Lindström N. Naltrexone for the treatment of amphetamine dependence: a randomized, placebo-controlled trial. Am J Psychiatr. 2008;165(11):1442–8. https://doi.org/10.1176/appi.ajp.2008.08020304.
73. Vocci F, Montoya I. Psychological treatments for stimulant misuse, comparing and contrasting those for amphetamine dependence and those for cocaine dependence. Curr Opin Psychiatry. 2009;22(3):263–8. https://www.ncbi.nlm.nih.gov/pubmed/19307968. https://doi.org/10.1097/YCO.0b013e32832a3b44.
74. Rawson RA, Marinelli-Casey P, Anglin MD, et al. A multi-site comparison of psychosocial approaches for the treatment of methamphetamine dependence. Addiction. 2004;99(6):708–73. http://www.ingentaconnect.com/content/bsc/add/2004/00000099/00000006/art00007. https://doi.org/10.1111/j.1360-0443.2004.00707.x.

Steroids, Dissociatives, Club Drugs, Inhalants, and Hallucinogens

13

Mashal Khan and Anil Thomas

High-Yield Review Points

- Anabolic-androgenic steroid use is common among men, especially those negative bodily perceptions, and their use comes along with adverse psychiatric and medical effects affecting multiple body systems.
- Inhalants, used most commonly by adolescents, vary in their pharmacological properties, though most fall into one of several categories: volatile hydrocarbons, nitrous oxide, or nitrates.
- Hallucinogens are a pharmacologically diverse group of substances that cause an alteration in sensory perception, mood, and cognition and include, though are not limited to, lysergic acid diethylamide (LSD); psilocybin (mushrooms); N,N-dimethyltryptamine (DMT); mescaline; and salvia
- Dissociative anesthetics exert their psychoactive effects by acting as antagonists at the NMDA receptor and produce a dissociative state with a greater degree of cognitive and neurological impairment than that produced by the classic hallucinogens.
- Falling under NIDA's classification of "club drugs," being able to recognize the intoxication and withdrawal symptoms, as well as the treatment, of both MDMA and GHB are critical.

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Anabolic-Androgenic Steroids (AAS)

Introduction

Anabolic-androgenic steroids (AAS) is a class of hormones that includes testosterone and its synthetic derivatives. Similar to testosterone, these compounds bind to the androgen receptor and produce both anabolic (muscle-building) and androgenic (masculinizing) effects to a varying degree. These drugs are used therapeutically for various conditions, largely utilizing the anabolic and/or androgen enhancement properties. These compounds have been used in higher than prescribed doses for physical or performance enhancement by weightlifters, bodybuilders, and other athletes, and they have been abused.

Epidemiology

In the United States, roughly 1% of the population (>three million) are estimated to have used AAS, and approximately one million men have experienced AAS dependence in the US. Even though the use of AAS may start as early as teens, the average age of the onset of use appears to be in the early 20s, the majority of users are men in their 20s–30s aiming to be lean and muscular; contrary to popular belief that use is relatively less prevalent among athletes [1]. Use is more common among men than females (>50:1), and long-term users are predominantly men; up to one third of users are thought to develop dependence [2]. Surveys of high school attending teenagers suggest a decline in use; i.e., self-reported lifetime prevalence among 8th–12th graders declined from 3.3% (2001) to 1.3% (2018) [3]. AAS use is rare among girls and women, though some anonymous surveys with high selection bias have suggested that substantial numbers of teenage girls have used AASs [4].

Body dysmorphic disorder, especially its subset muscle dysmorphia, is notably present among users of AAS; in two studies, 10 of 23 men (44%) [5] and 11 of 24 men (46%) [6] with muscle dysmorphia reported lifetime use of anabolic-androgenic steroids (AASs). These individuals also show elevated rates of mood and anxiety disorders, obsessive and compulsive behaviors, substance abuse, and impairment of social and occupational functioning.

Types of Anabolic Steroids and Sources

AAS are available in four forms: oral, intramuscular, topical (creams/gels), and patches. Among these, two forms, oral and intramuscular, are predominantly used outside of therapeutic indications. The oral form typically includes 17-alpha-alkylated androgens (such as stanozolol), which require daily dosing and are associated with a higher incidence of hepatotoxicity. IM formulations include testosterone esters (depot testosterone) and testosterone enanthate. These are slower to absorb than their oral counterparts; their effects last two to four weeks. Once in the body,

these compounds are metabolized by 5a-reductase to dihydrotestosterone (DHT) (which also contributes to male pattern baldness) and then by aromatase to estradiol (which contributes to gynecomastia) and neuro-steroids (which are responsible for psychoactive effects).

Users most often obtain androgens from the Internet. Suppliers often provide packages containing a variety of drugs: testosterone, synthetic androgens, aromatase inhibitors, human chorionic gonadotropin (hCG), and phosphodiesterase inhibitors. Some dietary supplements may also contain AAS.

Pharmacodynamics

Different types of AAS bind to androgen receptors with a varying degree of affinity. Androgen receptor complexes translocate to the cell nucleus, where they augment gene transcription, resulting in protein synthesis and leading to increased muscle mass. Psychoactive effects occur via AAS action at the membrane on the androgen receptor and via allosteric sites on the GABA receptor. Androgen metabolites, estradiol, and neurosteroids can also have psychoactive effects. The neurosteroid metabolites of testosterone (3-alpha- androstanediol) are a positive allosteric modulator of the GABA receptor and can have a potentiating effect on GABA receptors.

Patterns of Use

Individuals use these drugs for their anabolic properties in three common concepts. Often individuals titrate and taper off (pyramiding) using either individual or a combination of steroids (stacking). Androgen users often pyramid their doses in "cycles" of 6–12 weeks. Most users follow each "cycle" by an "off-cycle" phase for recovery. Stacks are intended to reduce unwanted side effects or for additive effect. Combinations used include both androgens and other drugs, such as growth hormone for additional anabolic effect, human chorionic gonadotropin (hCG) to counteract the reduction in testicular size resulting from high-dose androgen use, aromatase inhibitors to counteract gynecomastia, 5-alpha reductase inhibitors to prevent balding and acne, diuretics to promote water loss or to mask steroid misuse.

Presentation and Adverse Medical Effects

There are a number of specific situations that bring AAS users to the attention of clinicians. These include the following:

1. AAS dependence syndromes
2. Hypomanic and manic syndromes during AAS exposure
3. Syndromes of depression and anxiety associated with AAS withdrawal
4. Body image disorders associated with AAS use

5. Co-occurring substance use disorders
6. Medical conditions associated with long-term AAS use
7. Forensic situations, such as cases of AAS-induced violence or criminality

AAS users may experience the following adverse effects.

Cardiovascular The use of supraphysiologic doses of AAS is associated with a number of adverse effects, including dyslipidemia via the induction of hepatic lipase (reducing HDL); dose-dependent increase in left ventricular mass and related diastolic dysfunction [2, 7] hypertension; thrombosis, erythrocytosis, and polycythemia [8]; accelerated atherosclerosis related to dyslipidemias [2]; and increased risk of cardiac ischemia during peak exercise.

Endocrine Exogenous androgens result in the suppression of gonadotropins, impact the hypothalamic–pituitary–gonadal axis, causing feminization of men and masculinization of women; i.e., men may develop hypogonadism, reduced testicular size (reduced spermatogenesis and fertility) [9], erectile dysfunction, gynecomastia, and early onset prostatic hypertrophy. Women may experience shrinkage of breast tissue, oligomenorrhea/amenorrhea, hirsutism, clitoromegaly, and an irreversible deepening of the voice.

Hepatic Adverse effects concerning the liver are typically limited to oral AAS (i.e., 17a-alkylated agents) [2]. Hepatic peliosis (proliferation of sinusoidal hepatic capillaries that result in cystic blood-filled cavities), cholestatic jaundice, and hepatic neoplasms (rare) are related to cumulative dose and duration of use.

Neuro-psychiatric/behavioral Supratherapeutic doses most commonly present with aggression, anxiety, reduced inhibitory control, impulsive behavior, hypomania, and less commonly mania; psychotic reactions can occur. Alterations in the GABAergic system are thought to mediate many of the behavioral effects of AAS [10]. AAS exert a dose-dependent effect on the brain with high doses eliciting manic symptoms in normal men [11]. AAS withdrawal can present with mood swings, depression with suicidal behavior, and aggression with violent and assaultive behaviors, sometimes dramatic reductions in size and strength.

Musculoskeletal AAS users who aim to increase skeletal muscle mass over short periods are at risk of tendon rupture [2, 12] due to tendons' slower rate of adaptation to rapidly increased muscle mass. Specific to adolescents and the use of aromatized AAS is the premature closure of the epiphyses in teenage users, which may result in reduced final height.

Skin Frequently, individuals using AAS develop acne and oily skin; this is in part due to the overactivity of sebaceous glands and the related overproduction of skin surface lipids and the consequent increases in the population of cutaneous *Propionibacterium acnes* and *Staphylococcus aureus* bacteria [13]. Acne generally tends to resolve upon the cessation of AAS. Male pattern baldness may be seen in

both male and female users, is related to the effects of excess circulating DHT, and tends to be irreversible.

Assessment and Management

In the DSM-5 [14], misuse of AAS does not have a category of its own and falls under *Other (or Unknown) Substance Disorders*, the criteria is similar to the *Substance Use Disorder* criteria in the DSM-5; the severity of the use disorder is classified based on the number of criteria met. Within this category are subcategories of other substance use disorders, other substance intoxications, other substance withdrawals, other substance-induced disorders, and unspecified other substance-related disorders.

To improve clinical management, the history obtained should include information about use (i.e., stacks, pyramids, cycles, off-cycles), formulations and doses used, other pharmacological agents that they may have used to counter side effects (e.g., tamoxifen for gynecomastia, human chorionic gonadotropin for testicular atrophy, diuretics for edema, opioids for pain relief, and anxiolytics for anxiety), medical symptoms and their reversibility, and symptoms of mood, anxiety, substance use, and body image disorders.

A focused physical exam should include assessment for body composition (height, weight, body mass index, signs of rapid increase in lean body mass), skin (acne, male pattern baldness, needle marks, hirsutism, striae, or keloids), breasts (lactation, gynecomastia), genitourinary (testicular atrophy, clitoromegaly, enlarged prostate), and systemic signs of cardiac and liver disease.

Lab workup is based on presenting symptoms and possible organ systems affected, in addition to a hormonal panel (i.e., luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), testosterone (T), free testosterone (free T), sex hormone binding globulin (SHBG), and prolactin (PRL)); initial testing should include complete blood count (CBC), complete metabolic profile, creatine kinase (CK), lipid profile, prostate-specific antigen, urine drug screen, electrocardiogram (EKG), echocardiogram, and semen analysis. Tests may present with the following abnormalities: CBC (↑ RBC count, Hct and Hgb),liver function tests (↑ALT, AST, and LDH are often muscular in origin and may not indicate liver disease), muscle enzymes (↑CK, LDH, AST, and ALT may be elevated), lipid profile (may show ↓ HDL-C, ↑ LDL-C, ↑ or no change in total cholesterol and triglycerides), hormonal levels (↑testosterone and estradiol—with the use of testosterone esters, ↓testosterone—without the use of testosterone esters or during withdrawal, or ↓ LH and FSH), EKG (can show left ventricular hypertrophy), echocardiogram (can show decreased ventricular ejection fraction, impaired diastolic function), and semen analysis (↓sperm count and motility, abnormal morphology).

AAS detection is possible via the use of mass spectrometry-based testing of urine samples. Abuse should be suspected with high testosterone in association with suppressed LH and FSH levels. A T/E ratio of more than 4 can confirm testosterone abuse [2].

While addiction professionals can assist with treatments for the substance use disorder, management of AAS-induced adverse effects should be directed to specialists. Hypogonadism should be addressed and managed by consulting with endocrine specialists, and heart and liver problems can be directed to respective specialists.

There are limited data and lack of published clinical trials to support formal indications for treating AAS-related disorders; however, experts recommend utilizing cognitive behavioral therapies to address body image concerns, such as muscle dysmorphia, and to consider SSRI value in AAS users showing prominent and refractory obsessions related to body image. Depression is commonly seen in the withdrawal phase and treated with antidepressants, and if resistant ECT can be considered. Couples therapy is recommended for cases where the partner reports distress in living with the patient.

Inhalants

Introduction

Inhalants are volatile substances that produce chemical vapor that can be breathed in to induce a mind-altering/psychoactive effect and are believed to have specific pharmacological properties and effects in common. See Table 13.1 for common types of inhalants. The DSM-5 [14] identified volatile hydrocarbons as "inhalants" in its diagnostic criteria of "inhalant-related disorder." Inhalants are found in a variety of everyday products, such as paint, solvent, glue, aerosol propellant, and fuels. The DSM-5 classifies conditions related to either anesthetic gases, such as nitrous oxide, or nitrates, such as amyl, butyl, and isobutyl nitrate, under "other (or unknown) substance-related disorders." Nitrous oxide is used as a propellant in canisters of whipped cream, as a power booster in automobiles and motorcycles, and as an anesthetic agent for painful medical and dental procedures.

Volatile hydrocarbons can be categorized based on structure as aromatic, aliphatic, and halogenated hydrocarbons. Table 13.2 contains examples of each category, along with nitrous oxide and nitrites.

Table 13.1 Types of inhalants [15]

Inhalant type	Examples
Aromatic hydrocarbons	Petroleum products (gasoline and kerosene), propane, butane
Aliphatic hydrocarbons[a]	Toluene (used in paint thinner and model glue), xylene
Haloalkanes[a]	Hydrofluorocarbons, chlorofluorocarbons (including many aerosols and propellants)
Nitrates—amyl/butyl nitrites	"Poppers"
Nitrous oxide	Found in whipped cream canisters

[a]Volatile hydrocarbons

Table 13.2 Methods of administering inhalants [20]

Method of use	Description
Sniffing, snorting	Inhaling through the nose from the original container
Huffing	Inhaling through the mouth from the original container or inhaling from a chemically saturated rag held to the face or mouth
Bagging	Paper or plastic bag containing an inhalant being held over the mouth and nose or over the head, more commonly related to intentional self-harm or suicidal behavior
Dusting	Inhaling aerosol computer dusting spray via the mouth or nose
Glading	Inhaling air freshener

Epidemiology

Inhalant abuse is common among adolescents and less common among adults. According to the 2017 National Survey on Drug Use and Health (NSDUH) [16], 556,000 people (0.2%) aged 12 years or older used inhalants in the past month; use was most common in those ages 12–17 years. The most recent report by Monitoring the Future Study (MTF) [3] states that 8.7% of eighth graders, 6.5% of tenth graders, and 4.4% of 12th graders had ever used inhalants and that current inhalant abuse remains highest among eighth graders (i.e., 1.8% vs. 1.0 in tenth graders and 0.7% in 12th graders). Inhalant abuse has decreased over the last two decades; prevalence of 30-day use for grades 8,10, and 12 combined was 3.4%, 2.6%, and 1.1% in 1998, 2008, and 2018, respectively.

Among adults who are at risk for use are those with ready access to chemicals or anesthetics, such as doctors, nurses, factory workers, dentists, shoemakers, hair stylists, painters, and dry-cleaning workers. Nitrite use is prevalent among men who have sex with other men (MSM) [17] and utilized for its aphrodisiac properties.

Pharmacokinetics and Pharmacodynamics

Inhalants are highly lipid soluble. Upon inhalation, they rapidly cross both alveolar membranes and the blood–brain barrier to reach high concentrations in the brain while bypassing first-pass hepatic metabolism. The onset of symptom is within seconds of use, with peak plasma concentration 15–20 min after inhalation [15]. The mode of administration determines the inhaled concentration. Sniffing (inhaling through the nose from the original container) offers the lowest concentration, followed by huffing (inhaling by mouth from the original container or inhaling from a chemically saturated rag held to the face or mouth), and bagging (a paper or plastic bag containing an inhalant is held over the mouth and nose or over the head) offers the highest concentration. Most inhalants undergo elimination primarily through the lungs, usually unaltered by exhalation, although some inhalants, such as aromatics, alkyl nitrites, and methylene chloride, undergo hepatic metabolism, producing damaging and toxic byproducts such as free nitrites and carbon monoxide.

Inhalants are varied in their pharmacological properties. There is some overlap between volatile hydrocarbons and nitrous oxide that act as CNS depressants, although the mechanism of action is not entirely understood for most inhalants. The mechanism of action for volatile hydrocarbons is theorized to be similar to ethanol, with the stimulation of gamma-aminobutyric acid (GABA) and glycine alpha-1 receptors and the inhibition of the N-methyl-D -aspartate (NMDA) receptor, leading to inhibition in the CNS [18]. Nitrous oxide is theorized to exert its effect by mediating the release of endogenous beta-endorphins and direct binding on mu, delta, and kappa opiate receptors. In addition, it acts as an NMDA receptor antagonist [15]. Alkyl nitrites release nitric oxide, a potent vasodilator, that causes smooth muscle relaxation, a vital effect related to its abuse [19].

Clinical Features

Volatile Hydrocarbons

Immediate effects often include an initial stimulating "rush," followed by lightheadedness, disinhibition, and impulsivity. The effects of intoxication last minutes (typically 15–30 min) but can be extended by inhaling repeatedly. Euphoria is often followed by drowsiness, lethargy, headache, and sleep, especially with repeated cycles of inhalation use. Slurred speech, dizziness, diplopia, ataxia, and disorientation occur as the inhalant dose increases. With prolonged use, visual hallucinations and marked time distortion occur, which are cited as a motivator for continued use. Low-frequency users report more pleasurable experiences, whereas chronic users have mixed pleasurable and unpleasant or noxious experiences [18].

Table 13.3 below details toxic effects by systems. In addition to the effects mentioned, mortality has been noted in the context of asphyxiation or suffocation, choking on vomit, and careless or dangerous behavior in potentially dangerous settings. "Sudden sniffing death" [21] can also occur, though the mechanism

Table 13.3 Toxic effects of inhalants by organ system [15, 18]

	Toxic effects
CVS	Sinus bradycardia, increased QT dispersion [22], hypoxia-induced heart block, myocardial fibrosis, sudden sniffing death syndrome
Hematologic	Bone marrow suppression, leukemia, aplastic anemia
Pulmonary	Cough, wheezing, dyspnea, emphysema, pneumonitis
Dermatologic	Perioral rash/eczema, contact dermatitis, burns, angioedema, frostbite injury
Neurologic	Change in speech, drowsiness, nystagmus, peripheral neuropathy, sensorimotor polyneuropathy, tremor, ataxia, white matter degeneration, cerebellar degeneration
Gastrointestinal	Nausea, vomiting, diarrhea, abdominal pain/cramps, hepatotoxicity
Renal	Hypokalemia, acid-base disturbance, acute renal failure, Fanconi's syndrome, renal tubular acidosis
Neuro-psych	Apathy, depression, insomnia, poor attention, memory loss, dementia, psychosis

is unclear. It is theorized as an inhalant related increased myocardial cell depolarization and reduced conductivity, leading to anrhythmia paired with increased blood concentraiton of epinephrine [18].

Nitrites

The effects are instantaneous, brief, and intense. Nitrites cause vasodilation, resulting in a sudden surge of blood to the heart and brain. Users often experience a "head rush," which is a combination of elated mood or euphoria, lightheadedness, heat flush, and heightened sensual awareness [23]. The effects wear off within five minutes of use. Nitrites are also used to enhance sexual pleasure by prolonging penile erection and promoting anal sphincter relaxation.

Negative effects include headache, nausea, and syncope, which are related to the vasodilatory effects of nitrites. Nasotracheal irritation, sinusitis, and dermatitis may occur. Users can also develop methemoglobinemia, and acute impairment of oxygen delivery to tissues can present as headache, fatigue, dyspnea, and lethargy [15]. At higher methemoglobin levels (e.g., greater than 70%), respiratory depression, altered consciousness, shock, seizures, and death may occur [24]. Taking sildenafil with nitrites can cause severe hypotension, leading to syncope and cerebral or myocardial ischemia.

Nitrous Oxide

Its onset of action is two to three minutes, and the duration of effect is less than five minutes. Intoxication causes euphoria, dizziness, dulling of the senses, decreased pain sensation, and distorted audiovisual processes.

Nitrous oxide causes mild cardiac depression and indirect sympathetic stimulation [25]. Little change in blood pressure occurs because a mild increase in peripheral resistance offsets the mild cardiac depressant effect.

Users inhaling from a pressurized tank are at risk of pneumothorax [26]. Neurological and hematological effects are due to vitamin B12 inactivation by nitrous oxide; with chronic use it produces clinical effects that are similar to the subacute combined degeneration syndrome associated with pernicious anemia [27].

Assessment and Management

All patients suspected of inhalant use should have the following labs performed: complete blood count (CBC), pulse oximetry, EKG, basic metabolic profile (BMP), methemoglobin, and liver function tests (LFT). Urine toxicology does not identify inhalants; however, it may prove useful in screening for other substances. Specific findings that may indicate inhalant use include bone marrow suppression (associated with benzene); poor oxygen saturation, arrhythmias, hypokalemia, and hypophosphatemia (associated with toluene); methemoglobinemia (seen with nitrites); acidosis (seen with toluene); and liver and renal function abnormalities, particularly with halogenated hydrocarbons.

Management of acute inhalant intoxication is supportive care, primarily for cardiac and respiratory systems. Upon removing the source of intoxication, address any hypoxia with supplemental oxygen. Patients presenting in a coma with

respiratory depression require endotracheal intubation and mechanical ventilation. Arrhythmias are corrected based on commonly accepted guidelines. Electrolyte abnormalities should be corrected. Patients with methemoglobinemia should receive high-dose oxygen and IV methylene blue that accelerates the enzymatic reduction of methemoglobin (contraindicated in patients with G6PD deficiency) [28]. Chelation therapy may be required with lead toxicity, but the treatment has its limitations in only clearing inorganic lead and organolead (lead attached to carbon molecules) clear out over time [29].

Hallucinogens

Introduction

The term "hallucinogen" is an umbrella term used to describe substances that primarily cause an alteration in sensory perception, mood, and cognition. They are a pharmacologically diverse group of compounds that range from plant- and animal-sourced compounds to synthetic drugs. Organic sourced hallucinogens (plant, mushroom, or animal) have been used in religious rituals and recreationally for thousands of years [30], and examples include the genus *Psilocybe*, ayahuasca, peyote, and *Salvia divinorum*. Lysergic acid diethylamide (LSD) was the first synthesized hallucinogen by Albert Hofmann in 1938, and its psychoactive properties were discovered by accident five years later [31].

Also known as classical psychedelics, classical hallucinogens are organically sourced compounds and synthetic drugs that produce a varying degree of alterations in consciousness. They are divided into two chemical classes. Tryptamines, which are serotonin like in structure, include LSD, psilocybin, and dimethyltryptamine (DMT). Phenylethylamines include the drug mescaline [32]. They mediate effects via 5-HT2A receptor agonism or partial agonism [32]. Their effects are similar (LSD-like); however, they differ principally in time course (onset and duration of effects), which in turn depends on the particular substance, the dose, and the route of administration. Table 13.4 shows pharmacologic features of classic hallucinogens.

Epidemiology

Hallucinogen use occurs worldwide, although the prevalence is generally considered to be low relative to other drugs of abuse. LSD remains the prototypical hallucinogen and the most extensively studied of such drugs. Hallucinogens account for approximately 7% of United States emergency department (ED) visits involving illicit drugs. According to the 2017 National Survey on Drug Use and Health [16], 15.5% Americans ages 12 and older reported lifetime use of hallucinogens (9.6% LSD, 8.8% psilocybin, 2.1% peyote, 1.8% *Salvia divinorum*; 1.0% DMT, 2.2% phencyclidine (PCP),1.3% ketamine, 7.0% 3,4-methylenedioxy-methamphetamine (MDMA), 0.6% GHB). Rates of use in males is greater than females in each class;

Table 13.4 Pharmacological features of classic hallucinogens [20, 32, 45, 46]

	Typical dose	Onset (mins) (post ingestion)	Peak effects (hrs) (post ingestion)	Duration (hrs) (post ingestion)
Hallucinogen				
LSD	Oral: 25–200 μg	30–90	3–5	6–12
Psilocybin	Oral: 10 mg (20–30 g fresh mushrooms or 1–2 g dried)	20–30	1–2	6–8
DMT	Oral: 35–75 mg IV/smoked: 30–50 mg	20–60	1–2	2–8
Mescaline	Oral: 200–500 mg (6–12 dried buttons)	30–120	2–4	6–12

individuals under 21 years old have higher rates of use for serotonergic hallucinogens like LSD and psilocybin, whereas those over 20 years old have higher rates of use for PCP and ketamine.

LSD

LSD is the most potent classic hallucinogen (effects starting at 25 μg). Despite its potency, there is a considerable safety margin. It is often distributed and sold on small squares of blotter paper, colloquially referred to as "tabs" or "hits" that often contain 50 μg of LSD; a moderate dose (75–150 μg) will significantly alter state of consciousness [33].

The effects of LSD can vary widely, but typical perceptual changes include illusions, pseudo-hallucinations, and synesthesias, as well as alterations of thinking and time experience. Religious and mystical experiences may occur and can be produced reliably under controlled conditions [34]. Unwanted effects, such as dysphoria, anxiety, fear of insanity, and feelings that one is dying, can occur. These are colloquially referred to as a "bad trip" and usually resolve during the time course of acute drug action [35]. There are no documented human deaths from LSD overdose [33]. In some rare cases, acute psychotic episodes have occurred. Hallucinogen persisting perceptual disorder (HPPD) or "flashback," which is the intermittent reemergence of perceptual distortions weeks, months, or longer after the drug's effects have worn off, occurs in very low prevalence [36].

Psilocybin

Found in over 100 species of mushroom, including the members of genus *Psilocybe*, psilocybin was first isolated in 1958. Typically referred to as "shrooms" or "magic mushrooms," they can be consumed fresh or dried. It is intermediate in potency between LSD and mescaline, with a dose of 10–15 mg being roughly equivalent to 100 μg of LSD. The effects of psilocybin are very similar to those of LSD but of

shorter duration. Especially noteworthy are perceptual changes such as illusions, synesthesia, affective activation, alterations of thought, time sense, and body experience [37]. A mild headache is common for up to 24 h following psilocybin use.

DMT

DMT is a naturally occurring tryptamine, found in various plants, and is the active ingredient in ayahuasca, a traditional South American drink. Oral consumption of DMT leads to inactivation due to rapid metabolism by monoamine oxidase A (MAO-A) [38]. However, it can be rendered orally active by the administration of MAO inhibitors (MAO-I) before or along with DMT. Ayahuasca preparations utilize the same principle; the brew contains harmala alkaloids (MAO-Is), which prevent inactivation. DMT, on its own, is usually smoked or occasionally injected or insufflated. In smoked doses of around 40–50 mg, DMT produces a brief (<30 min) [38] and extremely intense experience that can involve complete loss of contact with reality, intense visual experiences, terrifying disorientation, incoordination, loss of ordinary sense of reality and self, mystical experience, and/or the experience of contact with other worlds or beings. The effects of ayahuasca are more prolonged (~4 h) and are generally similar to those of the classic hallucinogens described above [39]. Nausea and vomiting are common and considered to be related to the harmala alkaloids. Unlike frequent LSD use, tolerance to DMT does not seem to develop [38], but it is unusual for people to use it frequently due to the intense and sometimes overwhelming nature of the experience. Complications are infrequent, especially by the oral route, and also may not appear in clinical settings because of the very short duration of action of DMT. Individuals consuming ayahuasca or DMT along with an MAO-I are at increased risk of developing serotonin syndrome.

Mescaline

Mescaline (3,4,5- trimethoxyphenethylamine) is the active ingredient in peyote cactus, found in the Southwest US and Northern Mexico. The “dried button” (fleshy tops of the cactus) is ingested or crushed to a powder and prepared as a tea [40]. Mescaline is the least potent of the classic hallucinogens; a typical dose is between 6 and 12 buttons, and the effects are LSD like. Individuals frequently experience nausea or vomiting after ingestion. Users have reported experiencing recurring visual patterns, including stripes, checkerboards, angular spikes, multicolored dots, and fractals [41]. At higher doses, users may experience hyperthermia, headache, vomiting, hypotension, ataxia, diaphoresis, and depressed cardiac and respiratory function. These effects may precede the hallucinogenic effects, which may last 8–12 h.

Salvia

Salvinorin A, a diterpene alkaloid and kappa-opioid agonist, is the active ingredient in *Salvia divinorum*, an herb from the mint family that has been used in religious ceremonies for Mazatec Indians native to Oaxaca, Mexico. Salvia is pharmacologically distinct from classical hallucinogens in that it does not exert its psychoactive effect via serotonin; instead, it does so by stimulating the kappa-opioid receptor [42]. It is not a federally controlled substance and, as such, is sold in the form of leaves, which are available to recreational users at smoke shops and over the Internet. It can be chewed, smoked, vaporized, and ingested. The method of use can impact how long the effects last, with smoking or vaporizing having short effects (15–25 min), whereas chewing can have effects lasting 1–2 h. When chewed, the leaf mass and juice are maintained within the cheek area with absorption occurring across the lining of the oral mucosa (buccal); it has poor absorption via the GI tract [42]. Desirable subjective effects include elevation of mood, relaxation, feeling calm, introspection, mild dissociative effects, hallucinations, and synesthesia. At higher doses, users may experience dissociations, with intense hallucinatory effects and loosening contact with reality [43]. Larger doses are typically aversive.

Clinical Features

Mood can vary from euphoria and feelings of spiritual insight to depression, anxiety, and terror. Perception usually is intensified and distorted, with alterations in the sense of time, space, and body boundaries; illusions (visual and auditory distortions of perception) are common; true hallucinations (perceptions that do not have any basis in reality) are rare, while synesthesia (a blending of the senses wherein colors are heard and sounds are seen) may often be experienced [32, 44]. Reality testing is usually intact; however, some degree of confusion and disorientation may occur.

A "bad trip" usually takes the form of an anxiety attack or panic reaction, with the user feeling out of control. An experience of depersonalization may precipitate the fear of losing one's mind permanently. While higher doses are associated with more intense experiences, adverse reactions are less a function of the dose than of context and environment. Of note, mental "set" (mental state/intention/preparation of the person) and "setting" (environment) are thought to strongly influence the psychological content and emotional tone of the individuals' experience.

The acute somatic effects are typically mild to moderate and include nausea (+/− vomiting), dry mouth, chills, tremors, paresthesia, blurred vision, mild tachycardia, and hypertension [44]. Hallucinogen ingestion may also result in an acute toxic delirium that is characterized by delusions, hallucinations, agitation, confusion, paranoia, and inadvertent suicide attempts (e.g., attempts to fly or perform other impossible activities).

Assessment and Management

Hallucinogen abuse (other than PCP) can be diagnosed using the DSM-5 [14] criteria for *Other Hallucinogen Intoxication* or *Other Hallucinogen Use Disorder*; the criteria are similar to other substance intoxication and use disorder criteria in the DSM-5; the severity of the use disorder is classified based on the number of criteria met. Hallucinogen withdrawal syndrome is not a recognized phenomenon in the DSM-5; however, ~10% of hallucinogen users do report having withdrawal symptoms such as fatigue, irritability, and anhedonia. The DSM-5 describes hallucinogen persisting perception disorder (HPPD) as a disorder found in individuals with past exposure to hallucinogens experiencing flashbacks, vivid memories, or brief recurrences of sensory distortions reminiscent of intoxication during periods of sobriety.

Classical hallucinogen use rarely requires medical attention. Individuals seeking medical attention do so in the context of an overdose, acute anxiety or panic reactions, or accidental ingestion. Except in cases of delirium or overdose, the treatment of acute ingestion of a classic hallucinogen includes reassurance and a calm and safe environment. Reassuring patients that the drug is causing their anxiety and that the effects are transient should aid in partly mitigating symptoms. There is no role for medication in the treatment of uncomplicated hallucinogen withdrawal.

Severe reactions can include delirium or serotonin syndrome. In the case of agitation, dysphoria, and distress, benzodiazepines are the first line of treatment [47]; neuroleptics are a reasonable adjunct only if distress and concerning behaviors persist. Haldol may decrease the seizure threshold. Restraints are rarely necessary but recommended if there is an immediate danger of self-harm or assaultive behavior. Close observation of intoxicated patients and periodic monitoring of mental status are indicated due to rapid changes in mood and thought content during intoxication. Serotonin syndrome may occur in individuals who have ingested an ayahuasca brew or taken DMT with MAO-Is [48]. These individuals would present with increased autonomic activity (mydriasis, tachycardia, increased blood pressure), delirium, nausea, and vomiting and can be treated with the serotonin antagonist cyproheptadine. Following acute intoxication or severe reactions, short-term therapy is helpful for individuals who have had very intense, disturbing, or traumatic experiences; it can help them integrate their experience and identify/address any psychological sequelae.

At-risk individuals may experience recurrences of flashbacks with the initiation of selective serotonin reuptake inhibitors (esp. sertraline) [49]. Risperidone should be avoided; it has been noted to worsen visual disturbances and accompanying anxiety, presumably due to its alpha-2 presynaptic antagonism and noradrenaline release.

Benzodiazepines, clonidine, first-generation antipsychotics at low doses (esp. haloperidol), carbamazepine, and psychotherapy have shown to have positive therapeutic effects, although there is limited evidence to support their efficacy [50].

Table 13.5 Pharmacologic features of typical dissociative [20, 32, 45, 46]

	Typical dose	Onset (mins) (post ingestion)	Peak effects (hrs) (post ingestion)	Duration (hrs) (post ingestion)
Dissociative				
PCP	Oral: 2–6 mg IV/nasal/smoked: 1–3 mg	30–60 (swallowing) 2–5 (smoking)	1–4	4–8
Ketamine	Oral: 200–300 mg IN: 60–250 mg IM: 75–125 mg IV: 50–100 mg	15–20	0.5–1	1.5–2
DXM	Oral: 100–600 mg	15–30	2.5	4–6

Dissociative Anesthetics

Dissociative drugs cause a disconnection between thoughts, identity, consciousness, and memory. These heterogeneous group of chemicals can produce hallucinogenic effects. However, unlike the classic hallucinogens, they exert their psychoactive effects by acting as NMDA antagonists. Dissociatives include arylcyclohexylamines (phencyclidine (PCP) and ketamine), dextromethorphan (DXM), and nitrous oxide (discussed along with inhalants). These drugs produce a dissociative state with a greater degree of cognitive and neurological impairment than that produced by the classic hallucinogens. At higher doses, symptoms become more severe and can result in delirium, coma, and seizures. Table 13.5 shows features of dissociative anesthetics.

PCP

Initially utilized as an anesthetic agent, it was soon discontinued due to prolonged delirium, psychosis, agitation, and dysphoria after surgery [51]. Manufactured illicitly, it is available in various forms and a wide range of doses. In its purest form, phencyclidine (PCP) is a white crystalline powder that dissolves readily in water or alcohol; however, it is typically sprayed onto leafy material, such as cannabis, mint, oregano, tobacco, parsley, or ginger leaves and then smoked. It may also be insufflated and ingested orally. It is pharmacologically similar to ketamine, but it is more potent, longer acting, and more likely to produce seizures. A typical street dose is ~5 mg, with doses of 120 mg of PCP able to cause death.

PCP produces a range of intoxicated states that can be grouped into three stages [51, 52]. Stage I—conscious, with psychological effects and mild physiologic effects; Stage II—stuporous or in a light coma yet responsive to pain; and Stage III—comatose and unresponsive to pain. Intoxication at the mild Stage I desired by users is associated with few serious medical complications and would clinically present with euphoria, nystagmus (mostly horizontal but is one of a few drugs that

can cause vertical), tachycardia, increased blood pressure, disorientation, agitation, ataxia, dysarthria, numbness, increased salivation, and hyperreflexia. Higher stages are associated with severe medical effects, including hypertensive crisis, hyperthermia, seizures, rhabdomyolysis, acute renal failure, stroke, cardiac failure, coma, and death [51].

Ketamine

Ketamine is widely used as a general anesthetic (in combination with other agents) in animals and humans, in addition to its newer utilization in the treatment of pain and treatment-resistant depression [53]. It is pharmacologically similar to PCP and similarly a noncompetitive NDMA receptor antagonist [54] but less potent as an anesthetic with a faster onset and shorter duration of action. Primarily diverted from veterinary clinics, on the streets, ketamine is available as a liquid or a white powder and can be smoked, insufflated, injected, or taken orally.

The hallucinatory effects of ketamine last one hour or less, but the user's senses, judgment, and coordination may be affected for up to 24 h. Euphoria and hallucinosis peak effects occur in roughly 2.5 h. Doses of ketamine as large as 900–1000 mg given intravenously or intramuscularly are lethal. Although ketamine is often self-administered by insufflation, some are injecting it, increasing the risk for hepatitis C, HIV, and other infectious diseases [55]. Ketamine-induced coma occurs in a dose-dependent manner.

The clinical effects of ketamine are similar to PCP. Of note, in the short-term, ketamine causes problems with attention, learning, and memory. It also causes dreamlike states, hallucinations, sedation, confusion, speech problems, loss of memory, and movement problems progressing to immobility [56]. Elevated blood pressure, unconsciousness, and slowed breathing can occur. Large doses of ketamine may produce what users refer to as a "K-hole," which is a state reached when the user is on the brink of being fully sedated, often likened to an out-of-body or near-death experience. Although rare, overdose can cause death [57]. Ketamine can also cause kidney problems, stomach pain, and depression. Long-term ketamine use can cause damage to the bladder and urinary tract, which can result in a condition known as ketamine bladder syndrome [58]. The syndrome may cause ulcers in the bladder, blood in the urine, and incontinence.

DXM

Dextromethorphan (D-3-methoxy-N-methylmorphinan, DM, DXM) is the D-isomer of a codeine analog, methorphan. In contrast to the L-isomer, which is an opioid analgesic, DXM is not. In addition to NMDA antagonism, DXM has activity at the sigma receptor, which likely contributes to its therapeutic effects as a cough suppressant. DXM is available as an ingredient in more than a 100 different over-the-counter cough and cold medicines. Terms such as "robotripping," "tussin," or

"skittling" refer to illicit use. Antitussive dose ranges from 15 to 30 mg, recreational use can range from 240 to 1500 mg; clinically significant psychological and behavioral effects of DXM begin to occur at approximately five times the therapeutic dose. Its psychoactive effect overlaps with the effects of classic hallucinogens, including perceptual distortions, changes in the sense of time and space, alterations in body awareness, and spiritual experiences [59]. Psychoactive effects may be noted within 1 h of ingestion; these are dose related and are described by users as occurring in "plateaus" [60, 61]. At lower levels, i.e., 100–200 mg (1.5–2.5 mg/kg), users may experience euphoria and restlessness; 200–500 mg doses (2.5–7.5 mg/kg) result in exaggerated auditory and visual sensations and closed-eye hallucinations and imbalance; doses of 500–1000 mg (7.5–15 mg/kg) may result in altered consciousness, hallucinations, partial dissociation symptoms, and agitation; doses greater than 1000 mg (>15 mg/kg) can result in intense hallucinations, delusions, complete dissociation, and ataxia. Overdose can also cause respiratory depression, hyperthermia, and metabolic acidosis [60]. Additional ingredients in cough medicine (e.g., decongestants, antihistamines, acetaminophen, bromides) can cause other problems.

Assessment and Management

In the DSM-5 [14], diagnosis related to phencyclidine use can fall under *Phencyclidine Intoxication*, *Phencyclidine Use Disorder*, or *Other Phencyclidine-Induced Disorders* (includes diagnostic criteria for PCP-induced psychosis, mania, depression, anxiety, and intoxication delirium under specific subcategories), and the severity of the use disorder is classified based on the number of criteria met. Ketamine and dextromethorphan use can be diagnosed using the criteria of *Other Hallucinogen Use Disorder*.

Management of PCP intoxication should consider the level/stage of intoxication and aim at minimizing medical emergencies (seizures, hypertension, hyperthermia, and rhabdomyolysis) and behavioral consequences.

Initial assessment should follow the stabilization of breathing, circulation, and temperature. PCP is detectable in urine for up to eight days after use; other hallucinogens are not included in routine tests. Mild Stage I intoxication is best treated without medication. Sensory input should be minimal; unlike classic hallucinogens, reassuring and reality-oriented communication (talking down) rarely work with agitated PCP intoxication. Violent behavior can be prevented with physical restraints but can also increase agitation and the probability of rhabdomyolysis. Benzodiazepines are primarily used to treat agitation and seizures [51]. If agitation does not respond adequately to benzodiazepines, antipsychotics may be used. Antipsychotics should be used in moderation since they can lower the seizure threshold, cause dystonia, and exacerbate hyperthermia and anticholinergic symptoms. Tachycardia and hypertension may be treated with B-blockers, such as labetalol, or calcium channel blockers, such as verapamil and in cases of severe hypertension can be treated with IV nitroprusside. Standard cooling measures may

be applied in addressing hyperthermia. Rhabdomyolysis can be treated with IV fluids and diuretics.

Clinical support of distress associated with ketamine and DXM is similar to the methods used with classic hallucinogens. For DXM, which is often consumed orally, activated charcoal is effective for gastrointestinal decontamination [60]. Naloxone (an opioid antagonist) has been recommended for the treatment of respiratory depression in the context of DXM overdose [62]. DXM toxicity may result from the other ingredients found in cough or cold preparations (e.g., acetaminophen, pseudoephedrine, phenylephrine, guaifenesin, antihistamines). The evaluation and treatment of patients with suspected DXM overdose must attend to the possibility of acetaminophen or other concomitant toxicity.

Club Drugs

The term "Club drugs" is inclusive of a range of compounds, including various hallucinogens, stimulants, sedatives, and other drugs that have been associated with use at bars, nightclubs, concerts, and parties. The term is slightly misleading since drugs predominantly utilized in clubs, such as tobacco and alcohol, are not included in this category. NIDA identifies the following substances as club drugs: GHB, Rohypnol (flunitrazepam), ketamine, MDMA, methamphetamine, and LSD. Rohypnol and methamphetamines are covered under benzodiazepines and stimulants, respectively.

MDMA

Substance 3,4-methylenedioxy-methamphetamine (MDMA), commonly known as ecstasy, is a synthetic drug that is structurally similar to amphetamine. Categorized as an entactogen or empathogen due to its ability to evoke a sense of emotional openness and connection [63] (Nichols et al., 1986), it also elicits a unique mix of mood enhancement and stimulant-like and hallucinogenic effects.

MDMA exerts its psychoactive effect by promoting the release of serotonin, norepinephrine, and dopamine, preventing the reuptake of serotonin and inhibiting serotonin synthesis; its mechanism of action contributes to acute depletion of central serotonin. A typical dose of MDMA (75–150 mg) may take 30–60 min for onset and may last up to 4–6 h. Users report experiencing euphoria, increased sense of closeness toward others and empathy, energy, and reduced appetite; at higher doses, users may experience psychedelic hallucinogenic effects. Individuals who use MDMA often experience a "hangover" the day after use, characterized by insomnia, fatigue, drowsiness, sore jaw muscles from teeth clenching, loss of balance, and headaches. Users may experience minor adverse reactions from use, such as bruxism (grinding teeth), diaphoresis, nausea, blurry vision, tachycardia, and hypertension. Hyperthermia can occur as a result of MDMA's effects on the CNS, prolonged physical exertion, and environmental conditions. Hyponatremia may also occur and is often related to individuals drinking an excess amount of water [64].

Assessment and Management

Diagnosis is made using the DSM-5 [14] criteria under the heading of *Other Hallucinogen Use Disorder.* As with other substances, the severity of the use disorder is classified based on the number of criteria met.

MDMA intoxication typically comes to attention in cases of overdose, with the majority of the cases presenting with serotonin syndrome. Such patients should be evaluated emergently, and an ICU admission may be required. Cardiac monitoring and frequent monitoring of vital signs and mental status aid in its management. Activated charcoal should be administered if recent ingestion is suspected. Cooling measures are indicated in cases of hyperthermia. Dantrolene is sometimes used to treat hyperthermia due to MDMA ingestion, but its efficacy is not proven. Seizures, hypertension, and agitation are treated with benzodiazepines. In cases of rhabdomyolysis, intravenous fluids, alkalization of the urine, and furosemide are recommended [64].

GHB

Gamma-hydroxybutyric acid (also known as sodium oxybate) is a short chain fatty acid that occurs naturally in the brain. First synthesized in the 1960s, it was used as an anesthetic. Currently in the US, it is FDA approved as a schedule-III controlled substance for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy, and in some European countries it is used for the management of alcohol withdrawal and used off label to attenuate symptoms of opiate withdrawal. GHB has a wide range of formulations, use patterns, and associated health risks. It is used recreationally as a "club drug," to enhance muscle growth by bodybuilders, and by individuals for insomnia. The abuse potential of GHB is most likely the result of its anxiolytic, hypnotic, and euphoric effects. Recreationally, it is frequently used in combination with stimulants and/or alcohol.

Sources include supplements and industrial chemicals containing GHB analogs (GBL, BD), homemade GHB (recipes available on the Internet), and pharmaceutical formulations that can be prescribed and diverted from their intended use.

It is structurally similar to GABA and binds to endogenous GHB and GABA-B receptors. It modulates dopamine, opioid, serotonin, and noradrenaline release, as well as growth hormone secretion. Gamma-butyrolactone (GBL) and 1,4 butanediol (BD) are GHB precursors that upon ingestion are metabolized to GHB and have the same effect.

Effects of intoxication are comparable to alcohol and MDMA. Users report feeling euphoric, relaxed, disinhibited; elevated libido, energy, and stamina; and increased empathy and sensuality. Severe manifestations of GHB intoxication include CNS depression, hypoventilation, bradycardia, myoclonus, and seizures [65]. Users may also present with agitation and delayed delirium, as well as complications such as metabolic acidosis and Wernicke's encephalopathy.

Patterns of use vary significantly, from daily use among bodybuilders or nightly use among patients self-treating insomnia to binge use (every 30–60 min over

consecutive days) among recreational users. Tolerance develops quickly. Withdrawal phenomenon is associated with frequent daily dosing and with a total daily dose greater than 10 g [66].

Assessment and Management

Diagnosis is made using the DSM-5 [14] criteria under the heading of *Sedative, Hypnotic, or Anxiolytic Use Disorder*. As with other substances, the severity of the use disorder is classified based on the number of criteria met.

Presentation of GHB withdrawals is similar to that of alcohol and benzodiazepines in that dependent individuals may present with tremors, tachycardia, hypertension, diaphoresis, anxiety, agitation, and confusion. However, there is often more rapid and abrupt onset and more prominent delirium and psychosis (with paranoia, auditory and visual hallucinations); insomnia can be a notable feature.

Treatment of GHB toxicity and withdrawals consists of supportive care, including airway protection, cardiac and pulse oxygen monitoring, sedation for agitation, and treatment of complications. First-line treatment in managing withdrawal symptoms are high-dose benzodiazepines (up to 120 mg of diazepam daily). Barbiturates and propofol may be utilized in cases of benzodiazepine-resistant individuals [66]. Individuals using more than 30 g of GHB (or >15 g of GBL) per day may benefit from an inpatient management of their withdrawals. Severely depressed respirations indicate a need for intensive care treatment and mechanical ventilation. Once stabilized, oral benzodiazepines are commonly tapered off over 7–10 days.

Review Questions

1. Bob is a 24-year-old male with large muscles and acne who presents to a primary care clinic for acne medication. He talks about how much his self-confidence has improved since he's been "hitting the gym." What are the majority of the individuals using anabolic-androgenic steroids (AAS) in the US seeking to do?
   A. Compete in bodybuilding
   B. Improve athletic performance
   C. Improve physical appearance and strength
   D. Increase stamina
   E. Gain weight
   F. Decrease body fat

   Correct Answer: C

   Explanation: Over the past few decades, the trends in anabolic-androgenic steroid (AAS) use have changed. The majority of users are not athletes or body builders; rather, they are individuals who desire to increase and improve their physical strength and appearance.

   Reference: Kanayama et al. [67]

2. A 25-year-old male presents to a primary care clinic for his yearly physical. He reveals having used anabolic-androgenic steroids over the past six months to enhance his appearance. He denies having used any additional substance, drug, or supplement. Which of the following is most likely to be found on exam as a result of the use of high doses of anabolic androgenic steroids?
   A. Gynaecomastia
   B. Male-pattern baldness
   C. Hepatomegaly
   D. Testicular atrophy
   E. Hypertension
   F. Prostatic hypertrophy

   Correct answer: D

   Explanation: Exogenous AAS in high doses results in testicular shut down of testosterone production and consequent atrophy. The other options listed are possible outcomes of AAS use as well; however, testicular atrophy is directly related to its use and is the most common outcome.

   Reference: Rahnema et al. [68]
3. A 15-year-old male is brought to the pediatrician's office by his parents because of a rash. They suspect that it might be related to their son not eating well over the past few months. They have also noticed a recent decline in his school performance, and his teachers report a lack of attention during classes and overdue assignments. The patient denies changes in behavior and attributes his parents' concern to "being dramatic." On exam, the rash is perioral papules. Based on the presentation, use of which of the following substances is most likely?
   A. Cannabis
   B. Alcohol
   C. Ketamine
   D. Volatile hydrocarbons
   E. LSD

   Answer: D

   Explanation: Use of volatile hydrocarbons should be considered in persons showing intermittent changes compatible with inhalant use, together with an odor of organic solvents, inhalation paraphernalia, or the occasionally presence of perioral or perinasal papular "glue-sniffers" rash. Other options listed can contribute to some aspects of this patient's presentation but do not cause a perioral papular rash.

   Reference: Sadock et al. ([69], p. 1335)
4. Heidi is a 27-year-old female who enjoys nature and finds that drug use enhances her experiences. She estimates that she has used hallucinogens of some form or another about two to three times per month over the past ten years. She also reports that she is no longer able to live with her friends who find her religious

beliefs "bizarre." Which of the following is the mostly likely long-term consequence of regular and continued use of classic hallucinogens?

A. Insomnia
B. Anxiety
C. Depression
D. Impaired cognition
E. Flashbacks
F. Psychosis

Correct Response: E

Explanation: The most commonly associated long-term risk of classic hallucinogen use is hallucinogen persisting perception disorder, frequently referred to as "flashbacks." A flashback typically involves unexpectedly reexperiencing the perceptual, emotional, or somatic effects of a previous hallucinogen experience.

Reference: Halpern and Pope [36]

5. Heidi, in the question above, notes that she doesn't find that much happens when she takes hallucinogens now, and so she either does not take them or takes much higher doses than she used to enjoy. Marked tolerance may develop with repeated use of most classical hallucinogens. Which of the following is an exception to that trend?

A. LSD
B. Psilocybin
C. MDMA
D. Mescaline
E. DMT

Correct Answer: E

Explanation: Tolerance to LSD develops very rapidly, with significant decreases in the effect of subsequent doses after a single dose. Cross-tolerance exists among LSD, mescaline, and psilocybin, further evidence of their shared mechanism of action. This effect may be due to downregulation or internalization of 5HT2A receptors and is completely reversed within a week of abstinence. DMT may be an exception to this effect as marked tolerance is not observed. MDMA is not a classical hallucinogen.

Reference: Sadock et al. ([69], p. 1316)

6. A 20-year-old male presents for a mental health evaluation reporting distress in relation to recent onset visual distortions that are recurrent and unpredictable. He recalls having a similar experience while using LSD a year ago, acknowledges having used LSD multiple times during summer break a year ago, and has denied any substance use since. He reports recent stress and anxiety associated with upcoming midterm exams, and he denies any other symptoms. After a thorough workup and ruling out other causes, he is diagnosed with hallucinogen persisting

perception disorder. Which of the following treatment interventions can worsen symptoms in this patient?

A. Supportive Therapy
B. Risperidone
C. Alprazolam
D. Clonidine
E. Haloperidol

Correct Answer: B

Explanation: Risperidone (and possibly the atypical antipsychotics in general) should be avoided as a treatment option in HPPD as there is evidence that risperidone worsens the HPPD symptoms. Other interventions mentioned have shown to alleviate some of the symptoms of HPPD.

Reference: Sadock et al. ([69], pp. 1324–1325)

References

1. Kanayama G, Pope HG Jr. History and epidemiology of anabolic androgens in athletes and non-athletes. Mol Cell Endocrinol. 2018;464:4–13.
2. Pope HG Jr, Wood RI, Rogol A, Nyberg F, Bowers L, Bhasin S. Adverse health consequences of performance-enhancing drugs: an Endocrine Society scientific statement. Endocr Rev. 2013;35(3):341–75.
3. Monitoring the Future. National survey results of drug use. [Internet]. 2018 [cited 2019 May 2]. Available from: http://www.monitoringthefuture.org/data/18data/18drtbl5.pdf.
4. Kanayama G, Boynes M, Hudson JI, Field AE, Pope HG. Anabolic steroid abuse among teenage girls: an illusory problem? Drug Alcohol Depend. 2007;88(2–3):156–62.
5. Cafri G, Olivardia R, Thompson JK. Symptom characteristics and psychiatric comorbidity among males with muscle dysmorphia. Compr Psychiatry. 2008;49(4):374–9.
6. Olivardia R, Pope J, Hudson JI. Muscle dysmorphia in male weightlifters: a case-control study. Am J Psychiatry. 2000;157(8):1291–6.
7. Herschman Z. Cardiac effects of anabolic steroids. Anesthesiology. 1990;72(4):772–3.
8. Coviello AD, Kaplan B, Lakshman KM, Chen T, Singh AB, Bhasin S. Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. J Clin Endocrinol Metabol. 2008;93(3):914–9.
9. Coward RM, Rajanahally S, Kovac JR, Smith RP, Pastuszak AW, Lipshultz LI. Anabolic steroid induced hypogonadism in young men. J Urol. 2013;190(6):2200–5.
10. Henderson LP, Penatti CA, Jones BL, Yang P, Clark AS. Anabolic androgenic steroids and forebrain GABAergic transmission. Neuroscience. 2006;138(3):793–9.
11. Pope HG, Katz DL. Psychiatric and medical effects of anabolic-androgenic steroid use: a controlled study of 160 athletes. Arch Gen Psychiatry. 1994;51(5):375–82.
12. Kanayama G, DeLuca J, Meehan WP III, Hudson JI, Isaacs S, Baggish A, Weiner R, Micheli L, Pope HG Jr. Ruptured tendons in anabolic-androgenic steroid users: a cross-sectional cohort study. Am J Sports Med. 2015;43(11):2638–44.
13. Zomorodian K, Rahimi MJ, Taheri M, Asad AG, Khani S, Ahrari I, Pakshir K, Khashei R. The cutaneous bacterial microflora of the bodybuilders using anabolic-androgenic steroids. Jundishapur. J Microbiol. 2015;8(1).

14. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub; 2013 May 22.
15. Brouette T, Anton R. Clinical review of inhalants. Am J Addict. 2001;10(1):79–94.
16. 2017 National Survey on Drug Use and Health (NSDUH). Available from: https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2017/NSDUHDetailedTabs2017.htm#tab1-46A.
17. Dutta A, Uno H, Holman A, Lorenz DR, Wolinsky SM, Gabuzda D. Long-term nitrite inhalant exposure and cancer risk in MSM. AIDS. 2017;31(8):1169–80.
18. Tormoehlen LM, Tekulve KJ, Nañagas KA. Hydrocarbon toxicity: a review. Clin Toxicol. 2014;52(5):479–89.
19. Balster RL. Neural basis of inhalant abuse. Drug Alcohol Depend. 1998;51(1–2):207–14.
20. The Vaults of Erowid. Available from: https://www.erowid.org/psychoactives/.
21. Bass M. Sudden sniffing death. JAMA. 1970;212(12):2075–9.
22. Alper AT, Akyol A, Hasdemir H, Nurkalem Z, Güler Ö, Güvenç TS, Erdinler I, Cakmak N, Eksik A, Gürkan K. Glue (toluene) abuse: increased QT dispersion and relation with unexplained syncope. Inhal Toxicol. 2008;20(1):37–41.
23. Haverkos HW, Dougherty J. Health hazards of nitrite inhalants. Am J Med. 1988;84(3):479–82.
24. Coleman MD, Coleman NA. Drug-induced methaemoglobinaemia. Drug Saf. 1996;14(6):394–405.
25. Becker DE, Rosenberg M. Nitrous oxide and the inhalation anesthetics. Anesth Prog. 2008;55(4):124–31.
26. Garbaz L, Mispelaere D, Boutemy M, Jounieaux V. Pneumothorax following recreational inhalation of nitrous oxide. Rev Mal Respir. 2007;24(5):622–4.
27. Sanders RD, Weimann J, Maze M. Biologic effects of nitrous oxidea mechanistic and toxicologic review. Anesthesiology. 2008;109(4):707–22.
28. Romanelli F, Smith KM, Thornton AC, Pomeroy C. Poppers: epidemiology and clinical management of inhaled nitrite abuse. Pharmacotherapy. 2004;24(1):69–78.
29. Tenenbein M. Leaded gasoline abuse: the role of tetraethyl lead. Hum Exp Toxicol. 1997;16(4):217–22.
30. Schultes RE, Hofmann A, Rätsch C. Plants of the gods: their sacred, healing, and hallucinogenic powers. Rochester, VT: Healing Arts Press; 2001.
31. Hofmann A. LSD: my problem child. New York: Oxford University Press; 2013.
32. Nichols DE. Hallucinogens. Pharmacol Ther. 2004;101(2):131–81.
33. Passie T, Halpern JH, Stichtenoth DO, Emrich HM, Hintzen A. The pharmacology of lysergic acid diethylamide: a review. CNS Neurosci Ther. 2008;14(4):295–314.
34. Liechti ME, Dolder PC, Schmid Y. Alterations of consciousness and mystical-type experiences after acute LSD in humans. Psychopharmacology. 2017;234(9–10):1499–510.
35. Strassman RJ. Adverse reactions to psychedelic drugs. A review of the literature. J Nerv Ment Dis. 1984;172(10):577–95.
36. Halpern JH, Pope HG Jr. Hallucinogen persisting perception disorder: what do we know after 50 years? Drug Alcohol Depend. 2003;69(2):109–19.
37. Passie T, Seifert J, Schneider U, Emrich HM. The pharmacology of psilocybin. Addict Biol. 2002;7(4):357–64.
38. Carbonaro TM, Gatch MB. Neuropharmacology of N, N-dimethyltryptamine. Brain Res Bull. 2016;126:74–88.
39. Hamill J, Hallak J, Dursun SM, Baker G. Ayahuasca: psychological and physiologic effects, pharmacology and potential uses in addiction and mental illness. Curr Neuropharmacol. 2019;17(2):108–28.
40. Cassels BK, Saez-Briones P. Dark classics in chemical neuroscience: mescaline. ACS Chem Neurosci. 2018;9(10):2448–58.
41. Klüver H. Mescal, and mechanisms of hallucinations. University of Chicago Press; 1928.
42. Roth BL, Baner K, Westkaemper R, Siebert D, Rice KC, Steinberg S, Ernsberger P, Rothman RB. Salvinorin A: a potent naturally occurring nonnitrogenous κ opioid selective agonist. Proc Natl Acad Sci. 2002;99(18):11934–9.

43. El-Khoury J, Sahakian N. The association of Salvia divinorum and psychotic disorders: a review of the literature and case series. J Psychoactive Drugs. 2015;47(4):286–92.
44. Hollister LE. Effects of hallucinogens in humans. Hallucinogens: neurochemical, behavioral, and clinical. Perspectives. 1984:19–33.
45. Drug Enforcement Administration, US Department of Justice. Drugs and chemicals of concern. [Internet]. Available from: http://www.deadiversion.usdoj.gov/drug_chem_info/index.html.
46. Baselt RC. Disposition of toxic drugs in man. Chemical Toxicology Institute: Foster City, CA; 2000.
47. Taylor RL, Maurer JI, Tinklenberg JR. Management of bad trips in an evolving drug scene. JAMA. 1970;213(3):422–5.
48. Callaway JC, Grob CS. Ayahuasca preparations and serotonin reuptake inhibitors: a potential combination for severe adverse interactions. J Psychoactive Drugs. 1998;30(4):367–9.
49. Markel H, Lee A, Holmes RD, Domino EF. LSD flashback syndrome exacerbated by selective serotonin reuptake inhibitor antidepressants in adolescents. J Pediatr. 1994;125(5):817–9.
50. Martinotti G, Santacroce R, Pettorruso M, Montemitro C, Spano M, Lorusso M, di Giannantonio M, Lerner A. Hallucinogen persisting perception disorder: etiology, clinical features, and therapeutic perspectives. Brain Sci. 2018;8(3):47.
51. Bey T, Patel A. Phencyclidine intoxication and adverse effects: a clinical and pharmacological review of an illicit drug. Cal J Emerg Med. 2007;8(1):9.
52. Gorelick DA. Phencyclidine (PCP). In: Psychopharmacology, the fourth generation of progress. New York: Raven Press; 1995. p. 1767–76.
53. Gao M, Rejaei D, Liu H. Ketamine use in current clinical practice. Acta Pharmacol Sin. 2016;37(7):865.
54. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther. 2013;19(6):370–80.
55. Mathias R. Study suggests ketamine injection poses new disease risks for street youths. NIDA Notes. 2003;18(4):1–3.
56. Liu Y, Lin D, Wu B, Zhou W. Ketamine abuse potential and use disorder. Brain Res Bull. 2016;126:68–73.
57. Schifano F, Corkery J, Oyefeso A, Tonia T, Ghodse AH. Trapped in the "K-hole": overview of deaths associated with ketamine misuse in the UK (1993–2006). J Clin Psychopharmacol. 2008;28(1):114–6.
58. Srirangam S, Mercer J. Ketamine bladder syndrome: an important differential diagnosis when assessing a patient with persistent lower urinary tract symptoms. BMJ Case Rep. 2012;2012:bcr2012006447.
59. Reissig CJ, Carter LP, Johnson MW, Mintzer MZ, Klinedinst MA, Griffiths RR. High doses of dextromethorphan, an NMDA antagonist, produce effects similar to classic hallucinogens. Psychopharmacology. 2012;223(1):1–5.
60. Boyer EW. Dextromethorphan abuse. Pediatr Emerg Care. 2004;20(12):858–63.
61. Antoniou T, Juurlink DN. Dextromethorphan abuse. CMAJ. 2014;186(16):E631.
62. Chyka PA, Erdman AR, Manoguerra AS, Christianson G, Booze LL, Nelson LS, Woolf AD, Cobaugh DJ, Caravati EM, Scharman EJ, Troutman WG. Dextromethorphan poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol. 2007;45(6):662–77.
63. Nichols DE. Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens. J Psychoactive Drugs. 1986;18(4):305–13.
64. Hall AP, Henry JA. Acute toxic effects of 'Ecstasy'(MDMA) and related compounds: overview of pathophysiology and clinical management. Br J Anaesth. 2006;96(6):678–85.
65. P Busardo F, W Jones A. GHB pharmacology and toxicology: acute intoxication, concentrations in blood and urine in forensic cases and treatment of the withdrawal syndrome. Curr Neuropharmacol. 2015;13(1):47–70.

66. Kamal RM, van Noorden MS, Wannet W, Beurmanjer H, Dijkstra BAG, Schellekens A. Pharmacological treatment in γ-hydroxybutyrate (GHB) and γ-butyrolactone (GBL) dependence: detoxification and relapse prevention. CNS Drugs. 2017;31(1):51–64.
67. Kanayama G, Hudson JI, Pope HG Jr. Illicit anabolic–androgenic steroid use. Horm Behav. 2010;58(1):111–21.
68. Rahnema CD, Lipshultz LI, Crosnoe LE, Kovac JR, Kim ED. Anabolic steroid-induced hypogonadism: diagnosis and treatment. Fertil Steril. 2014;101(5):1271–9.
69. Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's comprehensive textbook of psychiatry. Tenth Edition, 50th Anniversary Ed. Philadelphia: Wolters Kluwer; 2017.

Behavioral Addiction

14

H. A. Colon-Rivera

High-Yield Review Points

- The co-occurrence of impulsive and compulsive features contributes to understanding behavioral and substance use disorders.
- Behavioral addictions resemble substance use disorders in many domains, including the natural history, phenomenology, genetic factors, and past responses to treatment.
- Family history and genetic information support heritability for behavioral addictions.
- Behavioral addictions are characterized by dysfunction in multiple brain areas and neurotransmitter systems.

Introduction

Defining components of behavioral addictions is the recurrent pattern of behavior despite adverse consequences, reduced self-control, compulsive engagement, and an appetitive urge or craving state prior to engaging in the behavior [1–3]. All behavioral addictions have a dysphoric state, analogous to withdrawal, and these usually involve irritability, restlessness, anxiety, and cravings. However, unlike in substance withdrawal, there are no life-threatening physical withdrawal symptoms from behavioral addictions.

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Dysfunction of financial, educational, occupational, and marital relations is common in behavioral addictions. The repetitive maladaptive engagement in these behaviors results in clinically significant impairment and/or distress in a person's level of function, similar to substance use disorders.

Gambling Addiction

Gambling disorder (GD) features repetitive, maladaptive gambling behavior, leading to severe adverse impact at the individual, familial, and social levels. People with GD are distinguished by impaired control over gambling, continuing with the behavior despite significant negative consequences [4]. The lifetime prevalence rate of GD is between 0.42% and 7.6% in adults [5]. Although gambling is viewed as an adult behavior, the prevalence of adolescent gambling problems is close to three times that of adults [6]. The specific environmental factors that may contribute to GD include trauma and social inequality, particularly in women [7]. Evidence exists of "telescoping" phenomena (starting with smaller intensity or frequency with more rapid escalation) in some cases of GD [8]. The Gambling Symptom Assessment Scale (GSAS) is an instrument used to assess the severity of gambling. The GSAS provides a score between 0 and 48. The GSAS scores are reflective of mild, moderate, severe, or extreme gambling disorder [9]. Nonpharmacological treatment includes the "Gamblers Anonymous," a mutual help fellowship based on the 12-step program of Alcoholic Anonymous.

Compulsive Buying or Shopping Addiction

This disorder is a condition in which people are preoccupied with shopping and suffer from recurrent buying impulses (or episodes) and lose control over their buying behavior [10]. This behavior has severe negative consequences, such as social, occupational, family, or financial difficulties. The prevalence ranges from 5.8% to 8.0% [11, 12]. Neurocognitive data suggest impairments in response inhibition, risk adjustment during decision making, and spatial working memory. Problems in these distinct cognitive domains support the similarities between compulsive buying and other behavioral and substance addictions [11, 12]. The Yale-Brown Obsessive-Compulsive Scale-Shopping Version is a measure of compulsive buying disorder treatment response and can be used to help with the clinical diagnosis of compulsive buying disorder.

Sex Addiction, Hypersexual Behaviors

These conditions involve preoccupation, unsuccessful attempts to control sexual behaviors, and sexual engagement despite adverse consequences. Symptoms and signs must be present for at least 12 months to meet the criteria for these disorders, and they must cause significant distress or impairment in different levels of function, such as family, finances, and social consequences. The prevalence of sex

disorders is estimated to be 3–6% of the general population [13]. The addictive sexual behaviors are more common in men, with onset usually in late adolescence.

Cue reactivity, or the level of sexual arousal to sex, is the most significant single predictor of sexual addiction, the severity of the habit, and impairment from the addiction.

The terms sex addiction, sexual addiction, addictive sexual behavior, compulsive sexual behavior, hypersexual disorder, sexual compulsivity, and sexual impulsivity describe roughly the same phenomenon. Other related terms include the following [14]:

(a) Paraphilias: are socially unacceptable behaviors that involve nonhuman objects, the suffering of self or the partner, children, or a nonconsenting person
(b) Nonparaphilic: is a compulsive sexual act with multiple partners, compulsive masturbation, frequent use of pornography, and compulsive sex acts within a consensual relationship
(c) Geo-locating social media: using online dating applications or other similar technologies to provide the proximity of users from each other with the objective of creating or recreating physical encounters

Eating Addictions

The correlations between eating addictions and substance use disorder are linked to the reward-responsive phenotype of eating [15, 16] with, and without, obesity. The lifetime prevalence of binge-eating disorder in American adults is 2.8%, based on DSM-IV criteria; it may be slightly higher with DSM-V new addition of the disorder and broadened appropiate defined criteria [14]. A World Health Organization survey of more than 24,000 adults in 14 mostly middle- and high-income countries found lifetime prevalence of binge-eating disorder, ranging from 0.2% to 4.7%, with the United States second in prevalence only to Brazil [17].

Eating addicting behaviors have a high negative urgency, high reward dependence, and lack premeditation [16]. People with eating addictions have a stronger brain-dopamine signaling strength compared to controls [15, 16]. Binge-eating disorder is an eating disorder that has been linked to high reward responsiveness in the ventral striatal activity during the anticipation of natural and artificial rewards systems. This linkage has been identified in the hormonal neurobiological circuit. Leptin and Ghrelin are crucial component of appetite and body weight regulation in the body. Leptin deficiency has been linked to a higher risk of abnormal eating habits by its effect on the arcuate nucleus of the hypothalamus [18]. Ghrelin administration into the ventral tegmental area (VTA) to the nucleus accumbens activates the reward system, suggesting that ghrelin may increase reward-seeking behavior enhancing the midbrain dopamine system [18].

The identification of patient with eating addiction is a key part of treating and preventing complications. The Yale Food Addiction Scale YFAS is the first assessment tool for addictive eating behavior and is based on DSM-IV criteria for substance dependence. Despite the "food addiction" naming, this scale assesses and identifies eating behaviors and patterns.

The prodrug lisdexamfetamine dimesylate (Vyvanse) is approved for the treatment of attention deficit disorders and is the sole FDA-approved drug for the treatment of moderate-to-severe binge-eating disorder. Another FDA-approved drug for ADHD treatment, atomoxetine, was significantly superior to placebo in reducing binge-eating behavior and achieving binge-eating remission in a small randomized controlled trial [19]. However, the use of atomoxetine in the treatment of binge-eating disorder is off-label.

Video Games and Internet Addiction

The Internet has become increasingly integrated in the activities of people's lives, but the degree to which we use the Internet or play video games determines if these behaviors are proper, problematic, or addictive. The defining characteristics of an Internet addiction include the dysregulation of arousal, impulsivity, and compulsivity. National surveys have shown a prevalence rate of 10–15% among young people in several Asian countries and of 1–10% in some Western countries [20, 21]. American samples show an Internet gaming disorder prevalence of 8.5% among those 8–18 years of age [22].

Some risk factors to develop the disorder are the presence of schizoid interpersonal tendencies, loneliness, introversion, low self-esteem, state and trait anxiety, and low emotional intelligence. The proposed criteria for gaming disorder feature behaviors that interfere in significant areas of functioning related to gaming, with persistent and recurrent gaming throughout at least 12 months that continues despite adverse consequences and in the setting of impaired control over gaming [17].

Neurobiology and Genetics

Behavioral addictions share genetic and environmental contributions in generatives studies and demonstrate similarities, as well as differences, at neurobiological levels. See Table 14.1.

Psychosocial Treatments

The research continues on psychodynamic therapy, motivational interviewing, and cognitive behavioral therapy effectiveness as treatments and their neurobiological underpinnings on behavioral addictions continues to develop. Many of these studies have small sample sizes and other limitations. Much of the current evidence-based treatments focused on cognitive behavioral therapy (CBT).

CBT is the most common psychological intervention for treating and reducing symptoms of behavioral addictions generally, and it is the most effective psychological intervention for treating and reducing problem gambling behavior specifically [25]. Studies have shown how CBT interventions increased insula activation from gaming-related cues and decreased connectivity between the orbitofrontal

Table 14.1 Behavioral addiction and key genetic and neurobiological points [5, 15, 18, 23, 24]

Behavioral addiction	Key results
Gambling	It is heritable. There is equivalent heritability between males and females. A variant exists in the 5-HTTLPR and monoamine oxidase A among males with gambling addiction. Initial genetic studies reported associations of pathological gambling With A1 allele of the dopamine (D)2 receptor gene (DRD2) Taq IA polymorphism. Preliminary positive clinical findings suggest that glutamate may have a role in impulsive and compulsive behaviors of gambling disorder. Twin studies indicate that 40–50% of the heritability can be predicted by genetic factors. It has an elevated concordance of attention deficit disorder.
Internet use	It is associated with polymorphisms of dopamine receptor genes and with the serotonin transporter and MAO-A polymorphisms. There is reduced D2-like receptor availability in dorsal striatum and no differences in ventral striatum in PET studies.
Video game playing	Taq IA polymorphism of DRD2 receptor gene and low-activity COMT alleles are more prevalent in compulsive video game players. There is increased metabolism in the middle orbitofrontal gyrus, reduced metabolism in the left precentral gyrus, and increased metabolism in the left caudate in PET scan findings.
Shopping	Compulsive shoppers are likely to have close family members with various psychopathology. No differences were seen in the frequencies of two 5-HTT gene polymorphisms. There is unclear response to selective serotonin reuptake inhibitors.
Sex	First-degree relatives are more likely to have SUDs. Limited positive clinical results suggest a possible role for serotonergic activity.
Eating	Low serotonin availability in the central nervous system could foster a voracious appetite for sugary and fatty foods. Variants of serotonin (5-hydroxytryptamine, 5-HT) receptors and type 3 (5-HT3) receptor genes may be related.

cortex and hippocampus, as well as between the posterior cingulate and motor-related brain regions [23]. These findings suggest that CBT decreases the strength of connectivity during exposure implicated in cue-induced craving in addiction behaviors [24]. CBT is combined with motivational enhancement therapy to move patients from ambivalence to engagement concerning behavioral change.

Group Psychotherapy

Group psychotherapy that uses a CBT model reduces the distress associated with compulsive and maladaptive behaviors. Impulse control training is a core component of behavioral addiction group therapy. Mutual help group models are available worldwide and are linked to favorable outcomes, particularly in conjunction with professional treatment for addictive behaviors [25].

Craving Behavioral Intervention

Based on cognitive neuroscience, the craving behavioral intervention was developed for patients with Internet gaming disorder to reduce cravings and enhance coping skills [23, 24]. It is conducted weekly in a group format with eight to nine participants. Topics for each weekly session include the following:

(a) Perceiving subjective craving
(b) Recognizing and testing irrational beliefs regarding the desires of doing the behavior
(c) Detecting craving and relieving craving-related negative emotions
(d) Coping with cravings and altering participant fulfillment of psychologic needs
(e) Learning time management and skill training for dealing with cravings
(f) Reviewing, practicing, and implementing skills
(g) Mindfulness training

Pharmacologic Treatments

Opioid Antagonists

Two randomized, double-blind, placebo-controlled trials have found significant improvement on behavioral addictions such as eating, sex, and gambling with naltrexone and nalmefene (not available in the US) compared with placebo [26, 27]. The opiate antagonists demonstrated a small but significant benefit and are the only evidence-based pharmacological treatments for some of the addictive behaviors [26, 27]. The medications appear to help reduce urges/cravings in the treatment of addictive behaviors.

N-acetylcysteine (NAC)

N-acetylcysteine (NAC) is an amino acid that is an over-the-counter dietary supplement. It has been reported to influence glutamatergic systems, particularly mGluR2 and mGluR3 receptors [28]. In an open-label study active, NAC was superior to placebo in maintaining diminished problem-gambling severity [28].

Glutamate and N-methyl-D-aspartate (NMDA) Receptor Modulators

Glutamate plays a pivotal role in behavioral addictions, and the N-methyl-D-aspartate (NMDA) glutamate receptor subtype serves as a molecular target for behavioral addictions [29, 30]. The release of glutamate by nerve cells leads to the rapid activation of these receptors and the depolarization of the neurons,

creating a behavior-related stimuli, producing related memories that will enable cues to drive addiction behaviors. The NMDA receptors are believed to mediate depolarization and/or induction of plasticity in individuals suffering from behavioral addictions [29–31].

Conclusion

Overall, much progress has been made to fully understand the environmental, genetic, clinical, and neuro-hormonal mechanisms underlying behavioral addiction. Neuroimaging and neuropsychological research have shown anatomical and molecular changes in brain structure. New understanding of underlying biological and environmental contributions to behavioral addictions allows for targeted psychologic and pharmacologic therapies in people suffering from these addictions. But the limited evidence-based research has improved clinical management and further clarified the understanding of the similarities and differences from character traits like impulsivity and compulsivity, from substance use disorders. Access to evidence-based treatments will reduce the isolation, stigma, and shame associated with behavioral addiction by showing the neurobiological basis and effective treatment for this disease. Understanding the characteristics of persons seeking help for and differences among patients suffering from behavioral addictions can help guide clinician decision making. Targeted multimodal and multidisciplinary treatments at both the individual and group levels with medication management if necessary, could help patients to recover and prevent complications from behavioral addictions and related disorders.

Review Questions

1. A 19-year-old college student has been acting "odd" for several months according to her parents. She takes too many "diet pills" at home. Her mother wants to know "if something is wrong with her brain." Which structure of the brain has been linked to positive reinforcement in behavioral addictions?
   A. Nucleus accumbens
   B. Striatum
   C. Globus pallidus
   D. Basal nucleus of Meynert
   E. Hypothalamus

   Correct answer: A. Nucleus accumbens

   Explanation: The nucleus accumbens is involved in behaviors elicited by incentive stimuli. These behaviors include natural rewards like feeding, drinking, sexual behavior, and exploratory locomotion. A rewarding event follows an essential rule of positive reinforcement. Moreover, dopaminergic, GABA, NMDA, and other gene and neurotransmitter-related gene polymorphisms affect both hedonic and anhedonia behavioral outcomes [30, 31].

2. You are seeing a 55-year-old married female presenting for physical examination. She says that she has tried to decrease her buying of lottery tickets during the past two months. "I think it is better than being a slot machine addict like my husband." From what we know about gambling, which of the following statements is most likely true in this case?
   A. She has higher rates of use or dependence on illicit drugs.
   B. She is at a higher risk than her husband of dying from suicide.
   C. She is twice as likely as her husband to meet the criteria for drug addiction in her lifetime.
   D. Her participation in gambling can escalate to addiction more quickly.

   Correct answer: D. Her participation in gambling, as a female, can escalate to addiction more quickly

   Explanation: Although more men have substance use problems, women tend to use or suffer from a behavior addiction at lower levels than men do, but they advance to a disorder more quickly. This phenomenon is called telescoping. Evidence exists of "telescoping" events (starting with smaller intensity or frequency with more rapid escalation) in some cases of gambling disorder. Women had a higher mean age at gambling initiation compared with that of men. According to the National Institute on Alcohol Abuse and Alcoholism, men are twice as likely as women to meet the criteria for drug addiction in their lifetime [8].
3. A 61-year-old man with a 19-year history of gambling disorder and worsening anxiety disorder is presenting to his monthly appointments; his doctor routinely asks him about his gambling behaviors. His reply is always the same: "I'm not giving up my gambling; my brother does it every day of his life and has no issues with it." Which one of the following stages of change best describes this individual's motivational level?
   A. Action
   B. Contemplation
   C. Precontemplation
   D. Maintenance
   E. Preparation

   Correct answer: C. Precontemplation

   Explanation: According to Prochaska and DiClemente's Stages of Change, precontemplation is characterized by either denial of the problem or an unwillingness to change.
4. A 21-year-old girl is concerned because her mother is spending too much time out "playing the horses." She also wants to know your thoughts about medication treatments. Which one of the following pharmacotherapies should be considered a first-line treatment for pathologic gambling?
   A. Naltrexone
   B. Lithium
   C. Topiramate
   D. Bupropion
   E. Amphetamine

   Correct answer: A. Naltrexone

Explanation: Naltrexone should be considered a first-line treatment for pathologic gambling, but there is currently no FDA-approved medication [2]. No significant difference has been shown between bupropion or mood stabilizers such as lithium and carbamazepine and placebo for pathological gambling.

5. A 16-year-old male presented to the emergency department complaining of agitation, aggressiveness, and disorganized behavior, which developed within a day after discontinuation of playing his favorite Internet video game. In American youth 8–18 years of age, what is the prevalence of video game addiction?
   A. 0.3%
   B. 8.5%
   C. 18%
   D. 31%

   Correct answer: B. 8.5%

   Explanation: Nationally representative American samples show an Internet gaming disorder prevalence of 8.5% among those 8–18 years of age [22].
6. Peter is a 57-year-old male who has been treated for depression successfully with fluoxetine for ten years, struggles with daily worries that affect his sleep and functioning, and goes to Alcoholics Anonymous every week to maintain recovery from alcohol use disorder. His partner Matthew has threatened to end their relationship if he does not stop going to the casino, spending more time at the casino than he plans, and "bailing on" important family functions to gamble instead. Which of the following disorders has the highest comorbidity with gambling disorder?
   A. Mood disorders
   B. Anxiety disorders
   C. Substance use disorders
   D. Schizophrenia

   Correct answer: C. Substance use disorders

   Explanation: Gambling disorder is highly comorbid with other mental health disorders, particularly substance use disorders, and shows a heritability rate of 50–60% [9].

References

1. Yau YH, Potenza MN. Gambling disorder and other behavioral addictions: recognition and treatment. Harv Rev Psychiatry. 2015;23(2):134–46.
2. Potenza MN. Should addictive disorders include non-substance-related conditions? Addiction. 2016;101:142–51.
3. Shaffer HJ, LaPlante DA, LaBrie R, Kidman RC, Donato AN, Stanton MV. Toward a syndrome model of addiction: multiple expressions, common etiology. Harv Rev Psychiatry. 2004;12:367–74.
4. Williams RJ, West BL, Simpson RI. Prevention of problem gambling: a comprehensive review of the evidence and identified best practices. Ontario Problem Gambling Research Centre: Guelph, ON; 2012.
5. Williams RJ, Volberg RA, Stevens RM. The population prevalence of problem gambling: methodological influences, standardized rates, jurisdictional differences, and worldwide trends. Ontario Problem Gambling Research Centre: Guelph, ON; 2012. [2014-12-28].

6. Shaffer HJ, Hall MN, Vander Bilt J. Estimating the prevalence of disordered gambling behavior in the United States and Canada: a research synthesis. Am J Public Health. 1999;89(9):1369–76.
7. Scherrer JF, Xian H, Kapp JM, et al. Association between exposure to childhood and lifetime traumatic events and lifetime pathological gambling in a twin cohort. J Nerv Ment Dis. 2007;195(1):72–8.
8. Potenza MN, Steinberg MA, McLaughlin SD, Wu R, Rounsaville BJ, O'Malley SS. Gender-related differences in the characteristics of problem gamblers using a gambling helpline. Am J Psychiatry. 2001;158(9):1500–5.
9. Kim SW, Grant JE, Potenza MN, Blanco C, Hollander E. The Gambling Symptom Assessment Scale (G-SAS): a reliability and validity study. Psychiatry Res. 2009;166(1):76–84. https://doi.org/10.1016/j.psychres.2007.11.008. Epub 2009 Feb 5.
10. Ridgway NM, Kukar-Kinney M, Monroe KB. An expanded conceptualization and a new measure of compulsive buying. J Consum Res. 2008;35:622–39.
11. Koran LM, Faber RJ, Aboujaoude E, Large MD, Serpe RT. Estimated prevalence of compulsive buying behavior in the United States. Am J Psychiatry. 2006;163:1806–12.
12. Mueller A, Mitchell JE, Crosby RD, Gefeller O, Faber RJ, Martin A, et al. Estimated prevalence of compulsive buying in Germany and its association with sociodemographic characteristics and depressive symptoms. Psychiatry Res. 2010;180:137–42.
13. Carnes PJ, Green BA, Merlo LJ, Polles A, Carnes S, Gold M. PATHOS: a brief screening application for assessing sexual addiction. J Addict Med. 2012;6(1):29–34.
14. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
15. Davis C. Compulsive overeating as an addictive behavior: overlap between food addiction and binge eating disorder. Curr Obes Rep. 2013;2(2):171–8.
16. Wolz I, Hilker I, Granero R, Jimenez-Murcia S, Gearhardt AN, Dieguez C, et al. "Food addiction" in patients with eating disorders is associated with negative urgency and difficulties to focus on long-term goals. Front Psychol. 2016;7:61.
17. World Health Organization. ICD-11 beta draft; 2016. Retrieved from http://apps.who.int/classifications/icd11/browse/l-m/en.
18. Barry D, et al. Obesity and its relationship to addictions: is overeating a form of addictive behavior? Am J Addict. 2009;18(6):439–51.
19. Reas DL, Grilo CM. Pharmacological treatment of binge eating disorder: update review and synthesis. Expert Opin Pharmacother. 2015;16(10):1463–78.
20. Mak KK, Lai CW, Watanabe H, Kim DI, Bahar N, Milen Ramos M, Young KS, Ho RCM, Aum NR, Cheng C. Epidemiology of Internet behaviors and addiction among adolescents in six Asian countries. Cyberpsychol Behav Soc Netw. 2004;17:720–8.
21. Wu XS, Zhang ZH, Zhao F, Wang WJ, Li YF, Bi L, Gong FF. Prevalence of Internet addiction and its association with social support and other related factors among adolescents in China. J Adolesc. 2016;52:103–11.
22. Gentile D. Pathological video-game use among youth ages 8–18: a national study. Psychol Sci. 2009;20(5):594–602.
23. Leeman RF, Potenza MN. A targeted review of the neurobiology and genetics of behavioural addictions: an emerging area of research. Can J Psychiatry. 2013;58(5):260–73.
24. Yip SW, Potenza MN. Treatment of gambling disorders. Curr Treat Options Psychiatry. 2014;1(2):189–203.
25. Jiménez-Murcia S, Granero R, Fernández-Aranda F, et al. Predictors of outcome among pathological gamblers receiving cognitive behavioral group therapy. Eur Addict Res. 2015;21(4):169–78.
26. Piquet-Pessôa M, Fontenelle LF. Opioid antagonists in broadly defined behavioral addictions: a narrative review. Expert Opin Pharmacother. 2016;17(6):835–44.
27. Bostwick JM, Bucci JA. Internet sex addiction treated with naltrexone. Mayo Clin Proc. 2008;83(2):226–30. https://doi.org/10.4065/83.2.226.
28. LaRowe SD, Myrick H, Hedden S, et al. Is cocaine desire reduced by N-acetylcysteine? Am J Psychiatry. 2007;164(7):1115–7.

29. Grant JE, Kim SW, Odlaug BL. N-Acetyl cysteine, aglutamate-modulating agent, in the treatment of pathological gambling: a pilot study. Biol Psychiatry. 2007;62(6):652–7.
30. Landa L, Machalova A, Sulcova A. Implication of NMDA receptors in behavioural sensitization to psychostimulants: a short review. Eur J Pharmacol. 2014;730:77–81.
31. Hopf FW. Do specific NMDA receptor subunits act as gateways for addictive behaviors? Genes Brain Behav. 2016;16(1):118–38.

Part III

Populations

Adolescents and Students

15

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High-Yield Review Points

- Alcohol is the most commonly abused substance in adolescents; marijuana closely follows. Studies indicate that the perceived risk of marijuana has decreased with legalization, the advertisement of medical uses, and perceived availability.
- The use of e-cigarettes has risen significantly compared with regular cigarette use.
- Screening tools, such as HEADSS, SBIRT, S2BI, BSTAD, have been shown to be effective for adolescents.
- Personality traits and pediatric temperaments are often cited as key risk factors to adolescent engagement in risky behaviors, including substance use.
- Treatment should include behavioral approaches, family engagement, and medication interventions. Current FDA-approved treatments for adults are not necessarily FDA approved in adolescents.

Introduction

Neurobiological, psychological, developmental, social, and environmental considerations contribute to adolescent substance use. Understanding the development of substance use in the child and adolescent population and utilizing appropriate early intervention and treatment decrease the risk of developing an adult substance use disorder [1]. From which substance is most abused to the limitations of screening

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and treatment options, assessing substance use in children and adolescents requires a different approach as compared with adults. While there are roughly 8000 child and adolescent psychiatrists in the United States, the child and adolescent population is 74.2 million, requiring adult psychiatrists to appropriately screen, diagnose, and treat this vulnerable population [2, 3]. Substance use prior to the age of 14 has been associated with a number of short- and long-term consequences. These include but are not limited to poor academic performance, including higher rates of dropout; substance use disorders in adulthood; unintentional overdose; suicide; accidents, including risk of TBI; increased risk of HIV and some forms of hepatitis; and memory disturbances [4].

Epidemiology

There has been a downward trend of substance use for most substances by American 8th, 10th, and 12th graders since the 1990s, according to the Monitoring the Future Study [5]. Of note, alcohol is the most commonly abused substance in this population, with roughly 2.3 million adolescents (13.3%) consuming one alcoholic beverage on a monthly basis and with 1.2 million adolescents participating in a binge-drinking behavior at least once a month. With the exception of marijuana and e-cigarettes, the majority of substances are declining in use; their prevalence affects many adolescents (Table 15.1)**.**

Marijuana is the second most commonly used substance in adolescents as roughly 1.2 million adolescents have reported using marijuana once a month. Studies indicate that the perceived risk of marijuana has decreased with legalization, the advertisement of medicinal uses, and perceived availability, which ultimately has led to use no longer decreasing [6]. While nicotine use has generally decreased among 8th–12th graders, the use of e-cigarettes has risen significantly compared with regular cigarette use [7].

Table 15.1 Prevalence of substance utilized in the past month from the National Survey on Drug Use and Health from 2016

Substance	Number of adolescents (ages 12–17)
Alcohol	2.3 million
Marijuana	1.6 million
Tobacco	855,000
Prescribed pain relievers	389,000
Inhalants	149,000
Hallucinogens	114,000
Tranquilizers	121,000
Stimulants	92,000
Cocaine	28,000
Sedatives	23,000
Methamphetamines	9000
Heroin	3000

Earlier use of illicit substances increases risk of developing a substance use disorder (SUD). The majority of those who have a substance use disorder started using before age 18 and developed their disorder by age 20.

Neurobiological Considerations

Understanding the basic principles regarding the neurobiological development of the brain will help clinicians conceptualize why children and adolescents may be drawn to substance use. The prefrontal cortex is the portion of the brain that is involved with executive function, which includes decision making, planning, response inhibition, and working memory [8]. Gray matter volume in the prefrontal cortex peaks between the ages of 11 and 13, leading to synaptic pruning, a process in which synaptic connections that are underutilized are "pruned" away. This process occurs much later in development as other portions of the brain undergo synaptic pruning before the prefrontal cortex [9]. Another aspect of neuronal development includes alterations in myelination where insulation of the neurons leads to faster cell signaling and processing. Similarly to synaptic pruning, myelination of the remaining and connected neurons occurs later in development, particularly in young adulthood [10]. Since synaptic pruning and myelination do not complete until later in young adulthood (late twenties), the consequence of an immature prefrontal cortex includes poor impulse control, increased risk-taking behavior due to lack of response inhibition, and difficulty with planning.

The tonic and phasic firing of dopamine also contributes to substance use in children and adolescents. Tonic dopamine firing, or low-frequency but sustained release of dopamine, leads to incentive motivation or the act of pursuing a stimulus that will provide an external reward [4]. In adolescents, the tonic firing of dopamine occurs at a faster rate than that of adults [11]. It is thought that this leads to adolescents being more likely to pursue illicit substances of use if they believe that there is an external reward associated with that substance. These external rewards would include peer approval, excitement for getting high, or taking away emotional pain.

Psychological and Developmental Considerations

The exact mechanism by which adolescents develop substance use disorders is not well understood and appears to be a complex function of biological, psychological, developmental, societal, and environmental considerations [12]. From a psychological and developmental perspective, adolescence is a period of experimentation and identity formation. It is during this period that children attempt to refine their sense of autonomy from their parents and simultaneously gain acceptance from peers [10]. It has been theorized that some adolescents use substances to seek this sense of independence from family members and social elevation from peers [10].

Risk Factors and Protective Factors

Personality traits and pediatric temperaments are often cited as key risk factors to adolescent engagement in risky behaviors, including substance use. Individuals who are prone to *sensation seeking* and *impulsivity* have been associated with an increased risk of adolescent alcohol use and an increased risk of substance use, respectively [13]. Other psychological risk factors include decreased ability to self-regulate when compared to peers and a difficult temperament [4, 13].

While research is limited and the exact way these factor influence risk is complex, some factors that have been identified as protective are increased competence, positive/easy temperament, and self-control [4, 12]. One hypothesis is that children's personality and temperamental factors influence the parenting that they receive and therefore the attachment/bonds that are later made [13].

Environmental (Familial, Peer, Community, School) and Societal Considerations

Firstly, with the transition out of primary school, there is a greater exposure to different peers and a new potential for acceptance into or rejection from new peer groups. Secondly, in later school years, there is usually more autonomy and less direct supervision from school authorities as classroom sizes tend to be larger and students are shared among a larger number of teachers [12]. Furthermore, amid all of these changes, there is a shift away from time spent with family members in favor of increased time spent with peers [11]. While adolescents are spending more time with peers, familial relationships and dynamics also play an important role in the risk of adolescent substance [12].

Societal factors that contribute to adolescent substance use include but are not limited to laws, policies, and popular media portrayal [12]. These considerations are further discussed below with regard to risk factors and protective factors for adolescent substance use.

Risk Factors and Protective Factors

Families play a key part in the risk of adolescent substance use. The roles that families play can best be broken down into familial use, attitudes, and parenting styles [13]. Higher rates of alcohol use have been described in adolescents with parents who use alcohol [12]. Additionally, parental attitudes toward substance use seems to have both a risk and a protective role [11]. Adolescents with parents who have negative views on substance use have lower rates of use, and conversely those who perceive their parents as having more permissive or even positive views of substance use have increased rates of use [13]. Furthermore, parental styles and parent–child relationship are a key component. A favorable parent–child relationship where the child feels cared for and accepted and receives adequate supervision and rules has

been associated with lower rates of adolescent alcohol use [12]. Conversely, inconsistent parenting, abuse, neglect, and high parent–child conflicts have all been associated with increased risk [11, 13]. Abuse from any perpetrator (familial or not) is associated with an increased risk of substance use [13].

Adolescents who are associated with peers who use substances and engage in other risky behaviors are more likely to use substances themselves, whereas adolescents who have peer groups that do not use substances or have negative views on substance use are less likely to use substances [12]. Additionally, popularity plays a role in risk, with students who self-identify as being popular having a higher risk of substance use. One theory for this is that these students may feel more pressured to use substances to gain a more positive view from their peers in order to maintain their popularity [10, 12].

Students with poor academic performances and who attend schools where drugs are readily available are at a higher risk for substance use, whereas students who identify as having a high level of school connectedness and academic competence are at a reduced risk [12]. From a community standpoint, lower socioeconomic status has been associated with a higher risk, although the exact mechanism is unknown [4, 13].

Societal views and norms also contribute to substance use risk. If a teen believes that substances are lethal or looked down upon largely by society, they are at lower risk of substance use [12]. This view can be developed via news and popular media portrayal of substance use, as well as laws surrounding the legalization and criminalization of substance use. One concrete example of this is that increased taxes on alcohol is associated with a decreased drinking rate among adolescents, but lower legal drinking age is associated with a higher drinking rate [13].

Risk and protective factors are further summarized in Table 15.2**.**

Table 15.2 Key risk and protective factors for adolescent substance use

	Risk factors	Protective factors
Individual	Impulsivity Sensation seeking ADHD Depression	Self-control Competence Easy temperament
Family	Child abuse and neglect Inconsistant parenting Permissive parenting style Parental substance use High level of parental–child conflict	Positive parent–child relations Clear parental expectations Negative perceived parental view of substance use Positive parental–child relationships
Peer	Maladaptive peer relationships Perception of popularity Gang affiliation	Friends who abstain from substances Belief that peers have negative view of substance use
School/ community	Poor academic performance Poverty Lower socioeconomic status Drug availability	School connectedness Academic competence Community attachment Illegal status/laws

Co-occurring Psychiatric Conditions

When evaluating children and adolescents for substance use disorders, it is also important to address mental health comorbidities, such as mood and anxiety disorders, attention deficit/hyperactivity disorder (ADHD), PTSD, which may place the youth at risk of developing or further increasing their substance use. When unrecognized or untreated, psychiatric comorbidities can significantly interfere with abstinence or harm reduction interventions addressing substance use.

ADHD

Evidence supports that youths with ADHD symptoms who are treated with stimulants have lower risks of developing a substance use disorder [14]. In addition, the younger the initiation of medications to address symptoms interfering with functioning, the greater the protective effect against developing a substance use disorder [15]. However, some other studies showed no benefit of medication in addition to CBT with motivational interviewing on the remission of substance use disorder, as measured by self-reported days of use and urine drug screen [16, 17]. A small naturalistic chart review study showed that bupropion reduced substance use, depression, and ADHD symptoms [18]. Pharmacotherapy for co-occurring ADHD and substance use disorders can be beneficial but must be considered on a case-by-case basis, weighing the risks of stimulant use, including diversion and misuse.

Conduct Disorder

Established therapy and behavioral treatments, not medications, have been shown to work well to reduce substance use in patients with conduct disorder. Multisystemic therapy (MST) is a well-established treatment for conduct disorder and criminal activity with evidence supporting its use in comorbid substance use disorders and conduct disorder. In addition, multidimensional family therapy (MDFT) has been shown to be effective for high acuity substance use disorders, as well as improved educational outcomes and decreased arrests.

Major Depressive and Bipolar Disorder

Pharmacotherapy in adolescents with depression has mixed evidence. A meta-analysis of randomized placebo-controlled studies showed that antidepressants showed significant effect on depression but minimal to no effect on substance use [19]. Studies highlight the importance of high-quality behavioral therapy (such as CBT and MI) and accurate diagnosis rather than specific antidepressants. Signs of changes in behavior and mood should also prompt consideration for a major

depressive episode or social/environmental factors such as bullying at school or difficulties in the family.

Few studies have focused on treatments for co-occurring bipolar disorder and substance use, partly because of the relatively low prevalence of this disorder in younger age groups. Very few studies have focused on pharmacotherapy, with a small randomized controlled trial showing Lithium benefits in patients with bipolar disorder and substance use [20].

Anxiety

There is little research in comorbid anxiety and substance use treatment in adolescents. Studies show promising results for behavioral family system therapy (BFST), as well as CBT with MI and mindfulness.

PTSD

Adolescents with PTSD and substance use are more likely to be female and of an ethnic minority status, highlighting the interrelated connections between social and environmental inequalities and mental health [21]. A randomized trial of Seeking Safety for adolescent girls with PTSD and substance use showed benefits. Mixed trauma-focused CBT and MST also has preliminary evidence in a small trial of sexually assaulted adolescents. Adolescents may seek substances to address symptoms of hypervigilance and hyperarousal when not utilizing other coping skills.

Risk Factors for Substance Use

Adolescents and the youth are faced with unique psychosocial issues that can influence their perception of substances and risk for use. Risks for the youth include family history (including genetics), family perceptions and parenting style, history of childhood maltreatment, and neglect. Genetics have been shown to explain more than half of the total variance in adolescent substance use. Parenting styles that are more authoritative, where parents set high expectations and clear rules about substance use, as well as achievable goals, are protective against substance use [22]. Parenting types that are less involved are more likely to lead to substance use. The number of adverse childhood experiences (such as abuse, neglect, trauma) has been shown to have a dose-response association to rates of drug use and subsequent development of a substance use disorders. In addition, LGBTQ youth face additional challenges such as stigma and estrangement from family, which contribute to higher rates of substance use disorders [23]. Therefore, interventions ought to address the histories of trauma, adverse childhood experiences, and family dynamics in the prevention of child and adolescent substance use.

Screening

Discussing substance use with adolescents and youths is a skill that requires taking a nonjudgmental attitude, showing a genuine interest, and forming a therapeutic alliance. Being clear about expectations and limits of confidentiality in the beginning of the interview, especially with respect to parental disclosures, will be important in forming trust.

The HEADSS mnemonic developed for primary care settings is a useful tool to explore topics that may be difficult to discuss. Clinicians should ask open-ended questions related to each of these domains, including home, education, activities, drug use, sexuality, and suicidality/mood. Other screening measures include the Screening, Brief Intervention, and Referral to Treatment (SBIRT); the Screening to Brief Intervention model (S2BI), which is endorsed by the American Academy of Pediatrics; and the Brief Screener for Tobacco, Alcohol, and Other Drugs (BSTAD). These tools have been shown effective for adolescents, however with varying sensitivity and specificity depending on age groups.

Treatment Considerations

Consent, Confidentiality, and Decision Making

Laws differ by state, and in most states adolescents younger than age 18 can consent for their own substance use treatment. Even in states that require parental approval, providers should seek assent from the patient. Providers should openly discuss with adolescents the limits of confidentiality prior to any information gathering. Sensitive information that does not pertain to safety should not be disclosed to parents without the patient's consent. However, treatment-related conversations are most effective when parents are also involved. The patient's support network is crucial to treatments that require frequent appointments, medication administrations, and harm reduction approaches.

Behavioral Approaches

Therapy and behavioral approaches have the most robust evidence in this population, compared with research on pharmacological treatment. Cognitive behavioral therapy (CBT) has been shown to be effective for reducing tobacco, alcohol, and marijuana use in adolescents. CBT courses tailored for youth according to their developmental stage are especially effective. Motivational enhancement therapy, the manualized version of MI, can be combined with CBT and involves short, problem-focused sessions aimed at resolving ambivalence and internal motivation. This technique is good for youths with limited attention capacity. The adolescent community reinforcement approach (A-CRA) uses cognitive and behavioral techniques to encourage prosocial activities toward recovery. Contingency management

is a very effective treatment that uses systems of incentives and rewards to encourage healthy behaviors, which can be combined with other behavioral treatments. The youth may also benefit from adjuncts to traditional clinical treatment, such as 12-step programs, residential programs, and youth community groups that offer peer support and facilitate identity formation separate from parents.

Family engagement is key to treatment success. Multidimensional family therapy (MDFT) is a technique developed for adolescent substance abuse that has benefits even years later based on research-derived evidence about adolescent and family development. MDFT is a manualized weekly family therapy that occurs over five to six months. It aims to change parenting behaviors and family interactions. Other family interventions shown to be effective for substance use include multifamily educational intervention (MEI), which involves more structure and psychoeducation compared to MDFT.

Pharmacotherapy Approaches

Treatment of adolescents with substance use disorders ought to include multiple approaches, addressing psychosocial issues, family dynamics, individual therapy, and 12-step programs, in addition to considering pharmacological interventions. Currently, medications, with the exception of an evidence base for buprenorphine for opioid use disorder, are not generally favored in the youth due to lack of evidence and lack of US FDA approval. Medications currently play a limited role beyond improving withdrawal and short-term intoxication.

Alcohol

Current FDA-approved treatments for adults are not formally approved in adolescents and the youth. Disulfiram has little evidence for efficacy in adolescents and is not preferred due to mixed results from the few existing studies [24]. Acamprosate also has limited data; however, one double-blind placebo-controlled study revealed significantly more abstinence among adolescents taking acamprosate after 90 days [25]. Naltrexone has only one published report of its use in adolescents involving five youths [26]. It was found to be well tolerated and effective at reducing alcohol consumption. Regarding treatments for acute intoxication and withdrawal, there are no adolescent or youth specific guidelines, and treatment is similar as that of adults. For all of these medications, use in adolescents regarding dosing and laboratory monitoring is the same as for adults.

Tobacco

For tobacco addiction, psychosocial treatments are the first line for adolescents. Unlike for adults, pharmacotherapy has shown limited results with the youth and

adolescents. There are currently no FDA-approved medications or nicotine replacement therapies (NRT) for adolescents under age 18; however, NRT and bupropion are the most commonly used in conjunction with psychosocial treatments in adolescents. Of NRT, research exists only for the patch and the gum in adolescents, which have some mixed results, but many show decreased withdrawal and decreased rates of cigarettes use [27].

Benzodiazepines

Abuse of prescription medications such as benzodiazepines is becoming increasingly common among the youth. Overdose and withdrawal can be life threatening, and currently there are no youth or adolescent specific guidelines. Treatment for withdrawal should follow general medical principles used in the management of adults. Currently, there is little research on youth-specific treatment for maintenance or long-term treatment. Management usually involves tapering the dose of the abused agent with psychosocial support, group, and individual therapy.

Review Questions

1. You are educating a parent on the development of the adolescent brain, and he asks you about why teenagers have high-risk behaviors compared with older populations from a biological perspective. What is an appropriate response?
   A. Maturation of the prefrontal cortex does not occur until the late teens, and that is why older teenagers participate in less-risky behaviors than younger teenagers.
   B. Phasic firing of dopamine release from the ventral tegmental area to the nucleus accumbens in adolescents is increased compared with adults, leading to pursuing stimuli.
   C. Synaptic pruning and myelination of the prefrontal cortex occurs much later compared with other portions of the brain, leading to the immature development of executive functioning.
   D. The prefrontal cortex matures first compared with other parts of the brain, and risk-taking behavior is solely based on environmental stimuli.

   Answer: C.

   Explanation: The prefrontal cortex is the portion of the brain that is involved in decision making, impulse control, and disinhibition. Maturation of the prefrontal cortex does not fully occur until the late 20s (A,D), which is why teenagers and young adults are more likely to participate in risk-taking behaviors. Maturation includes aspects of brain development, including myelination and synaptic pruning, which both also conclude in the latter stages of development (C). Furthermore, tonic phase release of dopamine (rather than phasic release)

occurs more frequently in adolescent populations compared with older populations, leading to the pursuit of stimuli that will lead to an external reward (D).

2. A 13-year-old boy comes to his clinic appointment. After the appointment, you meet with his mother separately, who tells you that she is concerned about his risk of abusing illicit substances. Which statement accurately reflects an appropriate response based on epidemiological data?
   A. While the risk of using substances is high, all illicit substance use has followed a general decline in terms of frequency of use within adolescent populations.
   B. While the frequency of use of the majority of illicit substances has declined, the frequency of marijuana use has increased among adolescent populations.
   C. A 13-year-old who drinks alcohol for the first time will have the same risk of developing a substance use disorder as a 17-year-old drinking alcohol for the first time.
   D. Marijuana has become the most commonly abused substance among adolescents at this time.

   Answer: B

   Explanation: General substance use among adolescents has decreased over the past two decades (A). However, the notable exception has been marijuana as rates have plateaued and even increased in some parts of the country (B). In terms of risk regarding the development of a substance use disorder, adolescents who utilize substances earlier have a higher risk of developing a substance use disorder that those who consume later (C). In terms of commonality, while marijuana is rising in terms of abuse, alcohol continues to be the most commonly used substance among adolescent populations (D).

3. You are seeing a 15-year-old at the department of juvenile justice for weekly clinic. He reports that he is considering drinking again with his friends when he is released. His history is remarkable for charges of aggressive assault, reported defacement of property, and frequent elopement from foster care. What intervention could you start that would reduce his risk developing a substance use disorder?
   A. Prescribe a stimulant and begin cognitive behavioral therapy.
   B. Prescribe an SSRI and begin multisystemic therapy.
   C. Begin multisystemic therapy.
   D. No intervention aside from supportive psychotherapy will reduce his risk.

   Answer: C

   Explanation: The patient appears to demonstrate multiple criteria for conduct disorder. In terms of curtailing risk of substance use with patients who have conduct disorder, multisystemic therapy has demonstrated the most benefit at reducing the risk of substance use disorder (C). While conduct disorder and ADHD are common co-occurring comorbidities, the patient does not appear to demonstrate ADHD criteria, and therefore a stimulant would not work (A). There is not enough data to support the diagnosis of MDD at this time (B), and supportive psychotherapy alone would be an inadequate treatment response.

4. Chloe, a 16-year-old female, is brought into your outpatient practice accompanied by her mother, who is concerned that her daughter has been falling behind in her school work and "wandering the streets at all hours of the night." You bring Chloe back to your office for interview, and her mother agrees to stay in the waiting room. When speaking to Chloe, it would be important early on to do which of the following?
   A. Demand to know what substances she is using.
   B. Request a list of the places that she is hanging out.
   C. Explain confidentiality and its limits.
   D. Provide the patient a cup for UTOX screening

   Answer: C

   Explanation: Treating adolescents and the youth involves unique challenges, such as the question of consent for treatment and confidentiality. Providers should openly discuss with adolescents the limits of confidentiality prior to any information gathering to aid in the establishment of rapport (**C**). While it may be important to determine the substances that Chloe may be using via subjective (A) and objective (D) measures, this should be obtained after establishing rapport and establishing the grounds of confidentiality. This is also true about obtaining further history, such as her overnight whereabouts (B).
5. Mrs. Johnson, a concerned mother of your 14-year-old patient, Kyle, presents to your office concerned about her son's potential for substance use, given that he will be entering a new high school in the fall. According to the National Survey on Drug Use and Health (NSDUH), which of the following is the most common substance used by adolescents?
   A. Alcohol
   B. THC
   C. Inhalants
   D. Prescription psychotropics

   Answer: A

   Explanation: Alcohol is the most commonly abused substance in this population, with roughly 2.3 million adolescents (13.3%) consuming one alcoholic beverage on a monthly basis. While inhalant use (C) is most commonly used by adolescents, it is not the most common substance used by this population. Cannabis and prescription psychotropics (B and D) are also not used as often as alcohol.
6. Tiffany, is a 15-year-old patient of yours who is brought to your clinic by her girlfriend, who is concerned about her recent alcohol use. The girlfriend reports that Tiffany has always been whimsical and a "free spirit," but things have worsened recently with her substance use. On interview, Tiffany tells you that she has started drinking to "drown out" her parents' arguments. She states that she feels like her parents "don't even care" about her activities or substance use. She also states that she really enjoyed school and has been "passing" grades. She has been very cautious in her decision making. Which of the following factors are associated with an increased risk of substance use for Tiffany?

A. Dismissive parenting style
B. Passing academic performance
C. Cautious
D. Supportive friend

Answer: A

Explanation: A number of developmental and psychosocial risk factors for substance use have been identified at the individual, familial, and community levels. Dismissive parental style, poor academic performance, impulsivity, and peer pressure are variables that have been associated with a higher risk of substance use.

References

1. Casey BJ, Jones RM. Neurobiology of the adolescent brain and behavior: implications for substance use disorders. J Am Acad Child Adolesc Psychiatry. 2010;49(12):1189–201.
2. Shatkin JP. Child & adolescent mental health: a practical, all-in-one guide. New York: W. W. Norton & Company; 2015. Print.
3. Trends C. Number of children. Bethesda, MD: Author; 2018. Retrieved from https://www.childtrends.org/indicators/number-of-children.
4. Cleveland MJ, Feinberg ME, Bontempo DE, Greenberg MT. The role of risk and protective factors in substance use across adolescence. J Adolesc Health. 2008;43(2):157–64.
5. Johnston LD, Miech RA, Bachman JG, et al. Monitoring the future national survey results on drug use, 1975–2016: overview, key findings on adolescent drug use. Ann Arbor, MI: University of Michigan Institute for Social Research; 2017.
6. Johnson SB, Blum RW, Giedd JN. Adolescent maturity and the brain: the promise and pitfalls of neuroscience research in adolescent health policy. J Adolesc Health. 2009;45:216–21. https://doi.org/10.1016/j.jadohealth.2009.05.016.
7. Sowell ER, Thompson PM, Holmes CJ, Jernigan TL, Toga AW. In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. Nat Neurosci. 1999;2(10):859–61.
8. Willuhn I, Wanat MJ, Clark JJ, Phillips PE. Dopamine signaling in the nucleus accumbens of animals self-administering drugs of abuse. Curr Top Behav Neurosci. 2010;3:29–71.
9. Ernst M, Luciana M. Neuroimaging of the dopamine/reward system in adolescent drug use. CNS Spectr. 2015;20(4):427–41.
10. NIDA. Principles of adolescent substance use disorder treatment: a research-based guide. National Institute on Drug Abuse website. https://www.drugabuse.gov/publications/principles-adolescent-substance-use-disorder-treatment-research-based-guide. January 14, 2014. Accessed October 18, 2018.
11. Schoenfelder EN, Faraone SV, Kollins SH. Stimulant treatment of ADHD and cigarette smoking: a meta-analysis. Pediatrics. 2014;133(6):1070–80.
12. National Research Council (U.S.), O'Connell M, Boat T, Warner K, Boat T, Warner KE, et al. Preventing mental, emotional, and behavioral disorders among young people: progress and possibilities. Washington, DC: National Academies Press; 2009.
13. Hawkins JD, Catalano RF, Miller JY. Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: implications for substance abuse prevention. Psychol Bull. 1992;112(1):64.
14. Thurstone C, et al. Randomized, controlled trial of atomoxetine for attention-deficit/hyperactivity disorder in adolescents with substance use disorder. J Am Acad Child Adolesc Psychiatry. 2010;49(6):573–82.

15. Riggs PD, et al. Randomized controlled trial of osmotic-release methylphenidate with cognitive-behavioral therapy in adolescents with attention-deficit/hyperactivity disorder and substance use disorders. J Am Acad Child Adolesc Psychiatry. 2011;50(9):903–14.
16. Dalsgaard S, Mortensen PB, Frydenberg M, et al. ADHD, stimulant treatment in childhood and subsequent substance abuse in adulthood — a naturalistic long term follow-up study. Addict Behav. 2014;39(1):325–8.
17. Bukstein OG, Horner MS. Management of the adolescent with substance use disorders and comorbid psychopathology. Child Adolesc Psychiatr Clin N Am. 2010;19(3):609–23.
18. Spas J, et al. All might have won, but not all have the prize: optimal treatment for substance abuse among adolescents with conduct problems. Subst Abuse. 2012;6:141–55.
19. Zhou X, et al. Efficacy and tolerability of antidepressants in the treatment of adolescents and young adults with depression and substance use disorders: a systematic review and meta-analysis. Addiction. 2015;110(1):38–48.
20. Geller B, et al. Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. J Am Acad Child Adolesc Psychiatry. 1998;37(2):171–8.
21. Chasser YM. Profiles of youths with PTSD and addiction. J Child Adolesc Subst Abuse. 2016;25(5):448–54. https://doi.org/10.1080/1067828X.2015.1081115.
22. Calafat A, Garcia F, Juan M, et al. Which parenting style is more protective against adolescent substance use? Evidence within the European context. Drug Alcohol Depend. 2014;138:185–92.
23. Goldbach JT, Tanner-Smith EE, Bagwell M, et al. Minority stress and substance use in sexual minority adolescents: a meta-analysis. Prev Sci. 2014;15(3):350–63.
24. Niederhofer H, Staffen W. Comparison of disulfiram and placebo in treatment of alcohol dependence of adolescents. Drug Alcohol Rev. 2003;22(3):295–7.
25. Niederhofer H, Staffen W. Acamprosate and its efficacy in treating alcohol dependent adolescents. Eur Child Adolesc Psychiatry. 2003;12(3):144–8.
26. Deas D, May MP, Randall C, et al. Naltrexone treatment of adolescent alcoholics: an open-label pilot study. J Child Adolesc Psychopharmacol. 2005;15(5):723–8.
27. Karpinski JP, Timpe EM, Lubsch L. Smoking cessation treatment for adolescents. J Pediatr Pharmacol Ther. 2010;15(4):249–63.

Women and Pregnancy

16

Natasia S. Courchesne and Stephanie A. Meyers

High-Yield Review Points

- Women who use substances may progress more quickly from first use to substance use disorder, may experience more intense withdrawal symptoms, and may respond differently to pharmacological treatments.
- Women face greater barriers to entering drug treatment, including greater substance-use-related stigma, family responsibilities, fear of child protective services involvement, and a greater likelihood of comorbid mood and anxiety disorders.
- Clinicians should adopt gender-responsive approaches when treating women who use substances, including motivational interviewing techniques, contingency management, community reinforcement approaches, and medication-assisted treatments (MATs) for those with opioid use disorders.

Introduction

Historically, substance misuse has been primarily conceptualized as a male problem, and as such, most substance use treatment research has focused on male populations. In more recent years, however, the scientific community has recognized that there are significant gender differences in substance use processes, trajectories, and

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related harms. A thorough discussion of the epidemiology, consequences of use, screening and diagnostic tools, and treatment considerations for women and pregnant women who use substances follows.

Epidemiology

Substance Use Among Women

Rates of substance use differ between men and women. Men are more likely to use almost every type of licit and illicit substance (including cannabis and misuse of prescription medications) [1], and their use is more likely to result in emergency department visits or overdose deaths compared to women [2]. Women tend to have higher rates of psychotherapeutic use of substances with potential of misuse (e.g., pain relievers, tranquilizers, stimulants, or sedatives, not including over-the-counter drugs), but men have higher rates of misuse [2]. Although men's rates of substance use and dependence are higher than those of women, women are as likely to develop a substance use disorder (SUD) as men [3]. Women also use smaller amounts of certain drugs for less time before they develop a SUD [2]. Research also shows that women may be more susceptible to cravings and relapse when compared to men, which are important components of the SUD cycle [2]. Among those in need of substance use treatment, men 18 years or older received slightly higher rates of treatment in the past year compared to women (2% vs 1%) [1]. Additionally, a higher proportion of females 12 years or older (4%) felt the need for treatment and made no effort to get treatment compared to males (2%). These findings highlight the importance of gender in substance use processes, trajectories, and treatment seeking. Table 16.1 shows treatment by substance for men and women.

Table 16.1 Substance use disorder and treatment in past year among those 18 or older, by gender: numbers in the thousands, 2017

	Total, *n* (%)	Men, *n* (%)	Women, *n* (%)
Substance use disorder			
Any substance use disorder	18,708 (7.6)	11,948 (10.0)	6760 (5.3)
Alcohol use disorder	14,062 (5.7)	9003 (7.5)	5059 (4.0)
Illicit drug use disorder	6804 (2.8)	4381 (3.7)	2423 (1.9)
Treatment for substance use disorder			
Any substance use treatment	3826 (1.5)	2461 (2.1)	1364 (1.1)
Alcohol use treatment	2369 (1.0)	1610 (1.3)	759 (0.6)
Illicit drug use treatment	2305 (0.9)	1497 (1.3)	808 (0.6)
Both illicit drug and alcohol use treatment	1116 (0.5)	827 (0.7)	290 (0.2)

Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2017

Substance Use among Pregnant Women

Among pregnant women, legal substances are the most problematic in terms of effect and magnitude. For example, smoking tobacco during pregnancy is estimated to have caused 1,015 infant deaths per year from 2005 through 2009 [2]. Alcohol consumption during pregnancy can cause miscarriage, stillbirth, and fetal alcohol spectrum disorder (FASD) and is the leading preventable cause of birth defects in the United States [4]. The 2017 National Survey on Drug Use and Health (NSDUH) report has found that alcohol and cigarette smoking rates during pregnancy increased from 10.6% and 8.3% to 14.7% and 11.5%, respectively, from 2016 [1]. Pregnant women's illicit substance use is less common and less problematic compared to alcohol and tobacco use [1]. However, according to the NSDUH 2017 report, illicit drug use in the past month among pregnant women 15 to 44 increased from 2016 to 2017 (6.3% to 8.5%) [1]. This includes both cannabis use (4.9% to 7.1%) and the misuse of psychotherapeutics such as pain relievers, tranquilizers, stimulants, and sedatives (1.4% to 1.8%) [1]. Given the legalization of cannabis in some states, cannabis use is expected to increase. In 2017, rates of cocaine (0.4%) and methamphetamine (0.1%) use among pregnant women were low, but opioid misuse (heroin or pain relievers) increased among this population from 2016 (1.2% to 1.4%). As a result of the current opioid epidemic, the number of women with opioid use disorder at labor and delivery has quadrupled from 1999 to 2014 [3], which has contributed to an increased incidence of neonatal abstinence syndrome (NAS) from 1.2 to 5.8 per 1000 hospital births per year from 2000 to 2012 [1].

Consequences and Considerations of Use in Women and Pregnancies

Physiological Consequences

Substance use during pregnancy poses concerns for the maternal, fetal, and neonate health and wellness. Many substances could potentially harm a fetus and increase the risk of long-term and fatal effects, such as congenital malformations, low birth weight for gestational age due to intrauterine growth restriction (IUGR), prematurity, microcephaly (small head circumference), prenatally acquired infections, complications of delivery, miscarriage, and sudden infant death syndrome (SIDS) [5]. Among women who smoke tobacco or cannabis, take prescription pain relievers, or use illicit substances during pregnancy, the risk of stillbirth is two to three times greater compared to women who do not use these substances while pregnant [6]. Neonates may also experience drug withdrawal (e.g., NAS) or neurobehavioral dysregulation, which presents following birth. The type and severity of NAS symptoms depend on the substance(s) used, how long and how often they were used, how the mother's body breaks down the substance, and if the neonate was born full term or prematurely. NAS can occur with a pregnant woman's use of substances such as

opioids, alcohol, nicotine, barbiturates, and amphetamines. Symptoms of NAS can develop immediately or up to 14 days post birth [7]. Some of these symptoms include diarrhea, excessive or high-pitched crying, irritability, increased heart rate, blotchy skin coloring, seizures, rapid breathing, trembling, vomiting, or slow weight gain [7].

Social Consequences

Women who use substances also face a number of unique social consequences as a result of their substance dependence when compared to their male counterparts. For example, women who use substances have been found to be more likely to have come from families in which one or more members are substance dependent, to have experienced more disruption in their families, to be in relationships with substance-dependent partners, to cite relationship problems as a significant contributor to their own substance use, and to be diagnosed with a mood or anxiety disorder [8]. In addition, women who inject drugs (WWID) have been found to be more likely to have been initiated into injection drug use by a male intimate partner, to be injected after their initiator, and to share injection equipment. These practices place women at increased risk of blood-borne infections like human immunodeficiency virus (HIV) and hepatitis C (HCV), bacterial infections, abscesses, and physical harm from being injected by someone who is intoxicated [9].

Legal Consequences

In addition to the aforementioned risks, and due to the illicit nature of most substances, women who inject drugs are at significant risk of involvement with law enforcement agencies and could face separation from their children if they are detained or incarcerated [9]. Among prisoners admitted to United States state prisons in 2012 with a sentence of more than 12 months, one in three women were admitted for drug offenses compared to one in seven men [9]. Additionally, as of 2015, more than two thirds of women in federal prisons were serving time for nonviolent drug offenses, and most of those women were single mothers [9]. This trend is of concern due to the research indicating that the prevalence of blood-borne infections and sexually transmitted infections are higher among women in prison when compared to men and that women prisoners experience more health problems than their male counterparts [9].

There are also a number of state laws and legal concerns that pertain to pregnant women who use substances, specifically. For example, as of 2019, there are 23 states and the District of Columbia that, under civil child welfare statutes, consider substance use during pregnancy to be child abuse. Three of these states, Minnesota, South Dakota, and Wisconsin, consider substance use during pregnancy to be grounds for civil commitment. Additionally, as of 2019, there are 25 states and the District of Columbia that require health care professionals to report suspected

prenatal drug exposure [10]. Furthermore, eight of these 25 states (Indiana, Iowa, Kentucky, Louisiana, Minnesota, North Dakota, Rhode Island, and South Dakota) require health care professionals to test for prenatal drug exposure if they suspect drug use [10]. Despite these policies, however, only 19 states have either created or funded drug treatment programs specifically targeted for pregnant women, and only 17 states and the District of Columbia provide pregnant women with priority access to state-funded drug treatment programs [10]. Due to the ever-changing nature of state laws, it is recommended that professionals refer to the Guttmacher Institute's website for up-to-date information on the specific state laws pertaining to pregnant women who use substances: https://www.guttmacher.org/state-policy/explore/substance-use-during-pregnancy.

Another important social consequence of substance dependence for women is involvement with Child Protective Services (CPS). Women who use drugs and WWID face a significant risk that disclosure of their drug use will lead to the notification of child protection authorities and that their children will be removed from their care [11]. Furthermore, once a report has been substantiated, the children of parents with substance issues are more likely to be placed in out-of-home care and to stay in care longer than other children [11]. The impact of child custody loss has been found to be akin to trauma for mothers who use substances, with many women reporting persistent posttraumatic stress disorder symptoms and increased substance use to cope with the separation [12]. These social consequences are important for clinicians to understand as they have implications for understanding the barriers to care that these women face and should guide approaches to treatment for this population.

Barriers to Care for Women Who Use Substances

Women have been found to be more likely than men to encounter barriers that prevent them from seeking or completing treatment [13]. For example, women are more likely to report having difficulty regularly attending treatment sessions due to family responsibilities and to report feeling stigma, shame, and embarrassment as a result of being in substance use treatment. Additionally, women are disproportionately affected by mood and anxiety disorders, which may further prevent women from seeking treatment [13]. Providing comprehensive services like housing, transportation, education, and income support has been found to significantly reduce substance use after treatment for both men and women, but a greater proportion of women are in need of these services [13]. Other barriers to care that have been cited by women include substance use itself, a lack of transportation, a lack of health insurance, financial barriers, and homelessness [14]. Pregnant women who use substances have also reported additional barriers to seeking prenatal care, including delays in discovering their pregnancy, a lack of doctors willing to initiate treatment with women in their third trimester, fear of involvement with CPS, and/or incarceration [14]. It is also important to note that women who use substances, including pregnant women, may have multiple, intersecting barriers that need to be addressed.

Screening and Diagnosis

Women

Most women presenting for primary care visits and/or prenatal care will not self-identify as being at risk for SUDs [15]. Due to the stigma and barriers that women who use substances face, clinicians serving women should ensure that they are creating an environment where women are comfortable discussing their substance use histories [15]. The American College of Obstetricians and Gynecologists (ACOG) recommends that all women who seek gynecological or maternity care be screened for substance use at least each year and that all routine SUD screenings be equally applied to all people regardless of age, sex, race, ethnicity, or socioeconomic status [16]. It is also recommended that brief interventions or motivational interviewing (MI) techniques be employed for those women who have high-risk substance use [15]. Screening Brief Intervention and Treatment (SBIRT), a comprehensive and integrated public health model for delivering early intervention services, has been recommended for addressing at-risk substance use in primary care settings for women [15].

The United States Preventive Services Task Force recommends a number of screening instruments for the screening phase of the SBIRT model. The Alcohol Use Disorders Identification Test (AUDIT), developed by the World Health Organization, has been validated for use with women [15]. The Drug Abuse Screening Test (DAST) has also been validated for use across diverse populations, including women involved in the criminal justice system [17].

Pregnant Women

Identifying SUDs in pregnant women early can minimize potential harm to both the mother and the neonate through appropriate intervention and treatment. For pregnant women, ACOG recommends that questions related to licit and illicit substance use should be carefully and sensitively posed and should include questions related to prescription opioids and other medications that may be misused [18]. Screenings should be conducted at the initial prenatal visit [18], and follow-up screenings should be conducted throughout the pregnancy (e.g., at each trimester). Recommendations also include screening women for alcohol use at least once a year and within the first trimester in pregnancy [19].

Although many screening and evaluation instruments for substance use exist, there is no optimal tool used to identify licit and illicit substance use among pregnant women specifically. A common approach used to elicit disclosure of perinatal substance use includes using nonjudgmental, open-ended questions during maternal interviews. Structured self-report instruments administered by providers have also been found to generate valid information pertaining to substance use and adverse pregnancy outcomes. The reliable and validated 4Ps Plus is used to assess alcohol and substance use among pregnant women [20]. Using five questions in four areas,

the 4Ps Plus asks about past and current substance use by the patient, her parents, or her partner. This particular screener is copyrighted and requires permission to be reproduced.

Screening instruments that have been developed and validated to screen for risky alcohol use among pregnant women include the T-ACE [21] and TWEAK [22]. Similar to the CAGE screener, the T-ACE has four questions that assess tolerance, being criticized for drinking, cutting down on drinking, and using alcohol as an eye opener. The TWEAK screener includes questions on tolerance, family and friend concerns, using alcohol as an eye opener, amnesia, and cutting down on drinking. In a systematic review, five studies comparing screening tools with structured interviews found that the highest sensitivity for identifying risky prenatal drinking included TWEAK, T-ACE, and AUDIT-C [23].

The CRAFFT questionnaire is validated for pregnant adolescents and young adults and consists of seven questions related to riding in a car with someone (or themselves) under the influence, using substances to relax, using substances on their own, forgetting things they did while using substances, being told to cut down by family or friends, and getting in trouble while using substances [24]. Finally, using CAGE-style questions, the Antenatal Psychosocial Health Assessment (ALPHA) tool can be used to screen for maternal substance use to identify psychosocial risk factors (e.g., family violence, postpartum depression) [25].

It is also common for women and pregnant women with a SUD to have co-occurring depression [26]. Depression should be assessed in pregnant women with SUDs at least on intake and between four and six weeks postpartum [27]. A history of trauma should also be assessed in women, including physical and sexual abuse as children. The degree of experienced trauma can be assessed with instruments such as the Trauma Symptom Inventory [28].

Approaches to Improve Outcomes and Treatment Considerations

Harm Reduction and Gender Responsive Treatment

Despite the wealth of research demonstrating that women have unique substance use-related trajectories, outcomes, and consequences, harm reduction and treatment options tailored directly toward women are still scarce. Gender responsive treatments (GRTs), however, have shown preliminary effectiveness in improving treatment outcomes [29]. GRTs have been defined, more specifically, as treatment modalities that take into account the unique needs and concerns of women who use substances (e.g., family responsibilities, increased levels of substance use-related stigma, higher prevalence of mood and anxiety disorders, etc.) [29]. One experimental pilot study of a GRT program for incarcerated women demonstrated that those in the GRT condition had greater reductions in substance use, were more likely to remain in residential aftercare, and were less likely to be reincarcerated 12 months after their release when compared to their control condition counterparts [29].

Other gender-focused suggestions for substance use treatment have included providing transportation and daycare options for women looking to access substance use-related services. Additionally, treatment options that are tailored for specific populations of women, such as those that have co-occurring SUDs and other psychiatric disorders (e.g., mood or anxiety disorders), have been recommended [29]. Others have also suggested that family-centered treatment services, like inpatient treatment options for mothers in which their children are able to stay with them, be implemented [11]. More information on treatment for women with SUDs is included in the following section.

Treatment for Substance Use Disorders Among Women and Pregnant Women

Treatment for SUDs may progress differently in women than for men. For example, women have reported a shorter duration of substance use prior to entering treatment, indicating that women's substance use tends to progress more quickly from first use to SUD [1, 30]. The optimal treatments for pregnant women with a SUD have been assessed in a small number of randomized trials with varying results [31]. In observational studies, engagement in treatment and prenatal care have been found to improve maternal and neonatal outcomes associated with maternal substance use [31]. MI techniques, with or without behavioral incentives, have been found to reduce maternal substance use [32]. A pilot study using MI in conjunction with cognitive-behavioral therapy (CBT) demonstrated decreases in substance use by about 50% in pregnant women [33]. Contingency management (CM) has the most extensive empirical data to support its use among pregnant patients, where it has been used to successfully improve treatment attendance and substance abstinence among pregnant women [34]. The community reinforcement approach (CRA) is less common among pregnant women with SUDs but has also demonstrated effectiveness [35]. A trial examining reinforcement-based treatment among pregnant women enrolled in comprehensive care for SUDs found that those treated with MI, CM, and CRA showed greater treatment utilization, improved abstinence from substance use, and shorter neonatal hospital stays compared to pregnant women who received basic substance use treatment [36].

Alcohol Although studies have shown that men and women metabolize alcohol differently [37], there appears to not be much difference in the outcomes associated with the treatment for alcohol (e.g., naltrexone) [38]. Brief psychotherapeutic interventions (e.g., MI) are the main treatment approach in pregnant women and have been found to reduce prenatal alcohol use [31]. Studies on MI to reduce alcohol use among pregnant women have shown either encouraging outcomes [39] or no change [40]. Most medications for the treatment of AUD are teratogenic or of unknown safety for the fetus, and so they are not typically recommended for use in pregnancy.

Tobacco Nicotine replacement therapy (NRT) (patch or gum) does not work as well for women as for men [41]. Nicotine withdrawal may also be more intense for women [42]. Among pregnant women, brief psychotherapeutic interventions are preferred in targeting smoking cessation and preventing relapse. However, this approach has seen modest success rates among this population [43]. Specifically, reduced smoking through MI has not been observed in methadone-maintained [44] or low-income [45] samples of pregnant women. CM, however, has been found to be successful in prenatal smoking cessation using financial incentives [46]. CM among this population has also been found to improve birth outcomes [47]. Data on pharmacological treatments for smoking cessation (e.g., varenicline, bupropion) among pregnant and postpartum women are limited. To date, the safety and efficacy of these types of treatments have not been well studied in clinical trials involving pregnant women. A recent systematic review and metanalysis found that of the 18 studies reviewed, there was no strong evidence to support any positive or adverse outcomes associated with the gestational use of bupropion or varenicline [48].

Cannabis Reducing cannabis use among women through MI, CM, and CRA therapies have been found to be successful; however, these approaches have had limited evaluation among pregnant women with a SUD [49, 50]. Consequently, there continues to be limited data on treatment for cannabis use disorders among pregnant women [51]. Further research on this population is needed to fill this gap and to address the potential impact resulting from changes in cannabis legalization and increasing cannabis use during pregnancy.

Stimulants MI, CM, and CRA are reliable evidence-based treatments for cocaine use in pregnant women [52]. CM is found to offer the greatest potential in reducing cocaine use among pregnant women [53]. In a randomized clinical trial on cocaine dependence among pregnant women or women with children, CM was found to be associated with a significantly longer duration of abstinence, an increased number of negative urine tests, and a higher proportion of abstinence in contrast to community reinforcement or 12-step programs [54]. Evidence-based pharmacological treatments for prenatal cocaine use are currently not available.

There are currently limited treatment options, however, for stimulants such as methamphetamines. An intervention that used reinforcement-based therapy (RBT) (an approach modeled after CRA) in conjunction with a women-focused intervention approach has been found to reduce methamphetamine use over time among pregnant women [55]. Interestingly, a reduction in methamphetamine use was observed in both the intervention and control groups. This relationship has also been observed elsewhere in a study investigating on RBT among cocaine and/or opioid users [32].

Opioids Rates of women seeking treatment for opioid use disorder (OUD) have increased over the last few decades and now are nearly equal to men [56]. Little

research on differences in treatment for OUD by gender is available. However, due to the complex nature of pregnancy and opioid use, attention to treatments for pregnant women with an OUD has increased. Traditional approaches to treating pregnant women with an OUD include medically assisted opioid withdrawal (e.g., gradually reducing opioid medications to prevent and reduce withdrawal and cravings until drug discontinuation), followed by inpatient or outpatient nondrug psychosocial treatments (peer support groups, counseling, and/or structured multimodel approaches). Due to the high proportion of women returning to opioid use and subsequent poorer outcomes, this approach is no longer recommended. Medication treatment with methadone or buprenorphine accompanied by supportive clinical follow-up is now considered the standard of care for pregnant women with an OUD.

As a full agonist, methadone has been used to treat pregnant women with an OUD since the 1970s. Methadone has been found to improve prenatal care, reduce fetal mortality, and improve fetal growth. In nonpregnant women, methadone treatment for OUDs has been found to show greater efficacy in reducing use and increasing abstinence compared with medical withdrawal and nondrug psychosocial treatments [57]. In pregnant women, methadone and medical withdrawal, followed by nondrug psychosocial treatment, has not yet been compared in a randomized trial. Avoiding medication-assisted treatments (MAT) reduces the direct medication risk to the fetus; however, high rates of women returning to illicit opioid use (59–90%) have been reported, resulting in greater adverse outcomes than those maintained on methadone [18].

The average half-life of methadone in women is 22–24 h compared to 8.1 h in pregnant women [58]. There is variable absorption during pregnancy and an accelerated metabolism of methadone with increased CYP3A4 expression by organs such as the liver, intestine, and placenta [59, 60]. However, as gestational age increases, clearance of methadone generally increases [61]. Higher doses or split doses are needed to maintain therapeutic effects.

Although methadone remains to be the standard of care for opioid agonist therapy during pregnancy, buprenorphine, a partial agonist, has also demonstrated positive outcomes. The Maternal Opioid Treatment: Human Experimental Research (MOTHER) trial randomly assigned 175 pregnant women with an OUD at eight international sites to treatment with either methadone or buprenorphine [62]. Of the 131 participants who gave birth while receiving either methadone ($n = 73$) or buprenorphine ($n = 58$), there was no significant difference in the percentage of neonates requiring treatment for NAS, peak NAS score, or head circumference [62]. However, there was a significant difference observed in the total amount of morphine needed to treat NAS (89% less) and length of neonate hospital stay (43% less) among those on buprenorphine compared to methadone. Though it was not found to be statistically significant, those treated with buprenorphine had a higher attrition rate compared to those on methadone (33% vs 18%). This may be due to the buprenorphine dosing protocol, which may not have been

strong enough to prevent withdrawal. Due to patient dissatisfaction and reduced tolerability of buprenorphine when switching from methadone, higher dropout rates have been observed when compared to methadone [62]. In a recent study, buprenorphine was also found to have shorter treatment durations, less medication needed for the treatment of NAS symptoms, and shorter neonate hospital stays [63].

Methadone or buprenorphine can be provided to prevent withdrawal symptoms and to reduce cravings throughout the pregnancy, postpartum period and can be continued for years. Women are especially vulnerable to treatment termination and opioid misuses during the postpartum period [64]. The long-acting injectable naltrexone (Vivitrol) is not considered a first-line treatment for OUD, especially in pregnant women, with limited data to support its safety to the fetus [63]. An additional impediment to the use of naltrexone among pregnant women could be the requirement of detoxification for at least seven days prior to administration [65]. Additional research is needed to determine the safety and benefits of naltrexone to treat pregnant women with OUD.

Substance Use and Breastfeeding

Mothers and infants impacted by SUD have a significant potential benefit in breastfeeding. As such, breastfeeding should be encouraged whenever possible. Because substances are excreted into breast milk and may have negative effects on breastfeeding infants, clinical protocols on safe breastfeeding have been developed by the Academy of Breastfeeding Medicine (https://www.bfmed.org/protocols) [66]. Mothers with a SUD should be discouraged from breastfeeding if they have not received prenatal care and relapsed in the last 30 days prior to delivery, among other circumstances. Currently, limited data exist on the effects of specific drugs in the breast milk by concentration on breastfeeding infants. Studies have found that breastfeeding among mothers on methadone or buprenorphine reduce the severity of NAS in opioid-exposed neonates [67, 68].

Conclusion

Substance use among women and in pregnancy continues to be a significant public health concern. Women who use substances have been found to have significantly different physiological, legal, and social consequences as a result of substance use when compared to men. It is recommended that clinicians utilize substance use screening measures that have been validated for women and/or pregnant women when assessing female patients that may have SUDs. In addition, it is recommended that clinicians create nonjudgmental environments and engage in gender-responsive treatment for women who use substances to decrease potential substance use stigma and barriers to treatment.

Review Questions

1. A 31-year-old female presents to her gynecologist for a healthy woman exam. The gynecologist asks about intimate partner violence, substance use, and mental health as part of his routine clinical screening. Which of the following psychiatric disorders are more common among women who use substances when compared to men who use substances?
   A. Attention-deficit/hyperactivity disorders (ADHD)
   B. Antisocial personality disorders
   C. Mood disorders
   D. Schizoaffective disorders
   E. None of the above

   Answer: C. Mood disorders

   Explanation: Women who use substances are disproportionately impacted by mood and anxiety disorders when compared to their male counterparts. Additionally, men who use substances are disproportionately impacted by antisocial personality disorder. No gender differences in ADHD or schizoaffective disorder comorbidity have been documented among people who use substances.
2. A 24-year-old woman with no reported past medical history presents to the emergency room with alcohol intoxication, and a screening, brief intervention, and referral to treatment is done. She is being transferred for alcohol detoxification prior to starting intensive outpatient treatment. Which of the following is *true* for women who use substances when entering treatment?
   A. Women may progress from first use to substance use disorder more slowly.
   B. Women may experience more intense withdrawal symptoms.
   C. Women do not respond differently to pharmacological treatments.
   D. Women may experience lower levels of substance use-related stigma.
   E. Women will not be retained in care longer or have better outcomes if they receive gender-responsive treatment.

   Answer: B. Women may experience more intense withdrawal symptoms

   Explanation: Research has indicated that women may experience more intense withdrawal symptoms. Additionally, research has indicated that women may progress from first use to a disorder *more quickly*, that they *do* respond differently to pharmacological treatments and experience *greater* levels of substance use stigma, and that gender-responsive treatment is particularly effective for women who use substances.
3. A 29-year-old pregnant female presents to her obstetrician for a prenatal care visit. The obstetrician would like to screen the patient for potential alcohol misuse without the patient feeling judged. Which of the following alcohol use screening measures have been validated and recommended for use with pregnant women?
   A. TWEAK, T-ACE, AUDIT-C
   B. CAGE, AUDIT-C, TWEAK
   C. T-ACE, AUDIT-C
   D. SMAST, CAGE, TWEAK
   E. T-ACE, CAGE

Answer: A. TWEAK, T-ACE, and AUDIT-C

Explanation: The TWEAK, T-ACE, and AUDIT-C have been validated and recommended specifically for use with pregnant women [23]. While the CAGE and the SMAST are validated measures of substance use, they have not specifically been validated for use with pregnant women.

4. A 32-year-old female presents at her gynecologist for a healthy woman exam. Her gynecologist, as part of obtaining a full patient history, would like to screen for potential at-risk substance use. The American College of Obstetricians and Gynecologists (in conjunction with SAMHSA and the United States Preventive Services Task Force) recommend which public health model for identifying and treating at-risk substance use among women?
   A. Screening Brief Intervention & Treatment (SBIRT)
   B. Residential treatment
   C. Outpatient treatment
   D. Smoking cessation classes
   E. Safe consumption facilities

   Answer: A. Screening Brief Intervention & Treatment (SBIRT)

   Explanation: The SBIRT public health model is currently recommended for assessing at-risk substance use among women. Other treatment modalities, including residential treatment, outpatient treatment, and smoking cessation classes are not sites that are useful in identifying at-risk use for women. Additionally, there are currently no sanctioned safe consumption facilities within the United States.
5. A 25-year-old pregnant female with opioid use disorder presents at her obstetrician for a prenatal care visit. Her obstetrician would like to provide treatment for her opioid use disorder as a part of her prenatal care regimen. Which of the following treatment methods have been proven to be effective in treating opioid use disorder in pregnant women?
   A. Medically assisted opioid withdrawal
   B. Naltrexone
   C. Medication-assisted treatment (methadone or buprenorphine)
   D. Medication-assisted treatment (methadone or buprenorphine) and supportive clinical follow-up
   E. Reinforcement-based therapy

   Answer: D. Medication-assisted treatment (methadone or buprenorphine) and supportive clinical follow-up

   Explanation: Both methadone and buprenorphine have demonstrated effectiveness in treating OUD in pregnant women. These medication-assisted treatments, paired with supportive clinical follow-up visits, are the current gold standard of care. Medically assisted opioid withdrawal is no longer recommended, and naltrexone has not sufficiently been investigated in pregnant populations. Additionally, reinforcement-based therapy techniques have been successful in treating stimulant use disorders, but no data currently exist demonstrating the effectiveness of this approach for OUD in pregnant women.

References

1. Center for Behavioral Health Statistics and Quality. 2017 National survey on drug use and health: detailed tables. Rockville, MD; 2018.
2. National Institute on Drug Abuse; National Institutes of Health; U.S. Department of Health and Human Services. Sex and gender differences in substance use; 2018. https://www.drugabuse.gov/publications/drugfacts/substance-use-in-women.
3. Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey. Exp Clin Psychopharmacol. 1994;2(3):244–68. http://psycnet.apa.org/buy/1994-45545-001. Accessed December 8, 2018.
4. National Institute on Alcohol Abuse and Alcoholism. Fetal alcohol exposure; 2015. https://www.niaaa.nih.gov/alcohol-health/fetal-alcohol-exposure. Accessed January 3, 2019.
5. MedlinePlus USNL of M. Neonatal abstinence syndrome: MedlinePlus Medical Encyclopedia. https://medlineplus.gov/ency/article/007313.htm. Published 2017. Accessed February 4, 2019.
6. Eunice Kennedy Shriver National Institute of Child Health and Human Development. Tobacco, drug use in pregnancy can double risk of stillbirth; 2013. https://www.nih.gov/news-events/news-releases/tobacco-drug-use-pregnancy-can-double-risk-stillbirth. Accessed January 15, 2019.
7. Hudak M, Tan R. Neonatal drug withdrawal. Pediatrics. 2014;129(2):2011–3212. https://doi.org/10.1542/peds.2014-0557.
8. Tuchman E. Women and addiction: the importance of gender issues in substance abuse research. J Addict Dis. 2010;29(2):127–38. https://doi.org/10.1080/10550881003684582.
9. Iversen J, Page K, Madden A, Maher L. HIV, HCV, and health-related harms among women who inject drugs: implications for prevention and treatment. J Acquir Immune Defic Syndr. 2015;69 Suppl 2(0 1):S176–81. https://doi.org/10.1097/QAI.0000000000000659.
10. Guttmacher Institute. Substance use during pregnancy. https://www.guttmacher.org/state-policy/explore/substance-use-during-pregnancy. Published 2019. Accessed November, 2019.
11. Child Welfare Information Gateway. Parental substance use and the child welfare system; 2014. https://www.childwelfare.gov/pubs/factsheets/parentalsubabuse/. Accessed December 4, 2019.
12. Kenny KS, Barrington C, Green SL. "I felt for a long time like everything beautiful in me had been taken out": women's suffering, remembering, and survival following the loss of child custody. Int J Drug Policy. 2015;26(11):1158–66. https://doi.org/10.1016/J.DRUGPO.2015.05.024.
13. Gender GCA. Use of substance abuse treatment services. Alcohol Res. 2006;29(1). https://pubs.niaaa.nih.gov/publications/arh291/55-62.pdf.
14. Roberts SCM, Pies C. Complex calculations: how drug use during pregnancy becomes a barrier to prenatal care. Matern Child Health J. 2011;15(3):333–41. https://doi.org/10.1007/s10995-010-0594-7.
15. Shogren MD, Harsell C, Heitkamp T. Screening women for at-risk alcohol use: an introduction to Screening, Brief Intervention, and Referral to Treatment (SBIRT) in women's health. J Midwifery Womens Health. 2017;62(6):746–54. https://doi.org/10.1111/jmwh.12659.
16. American College of Obstetricians and Gynecologists. Committee opinion number 633: alcohol abuse and other substance use disorders: ethical issues in obstetric and gynecologic practice. Obstet Gynecol. 2015;125:1529–37.
17. Yudko E, Lozhkina O, Fouts A. A comprehensive review of the psychometric properties of the Drug Abuse Screening Test. J Subst Abus Treat. 2007;32(2):189–98. https://doi.org/10.1016/J.JSAT.2006.08.002.
18. American College of Obstetricians and Gynecologists. Committee opinion number 711: opioid abuse, dependence, and addiction in pregnancy. Obstet Gynecol. 2017;119:1070–6.
19. American College of Obstetricians and Gynecologists. Committee opinion 496: at-risk drinking and alcohol dependence: obstetric and gynecologic implications. Obstet Gynecol.

2011;118:383–8. https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Health-Care-for-Underserved-Women/At-Risk-Drinking-and-Alcohol-Dependence-Obstetric-and-Gynecologic-Implications. Accessed January 15, 2019.
20. Chasnoff IJ, Wells AM, McGourty RF, Bailey LK. Validation of the 4P's Plus© screen for substance use in pregnancy validation of the 4P's Plus. J Perinatol. 2007;27(12):744–8. https://doi.org/10.1038/sj.jp.7211823.
21. Sokol RJ, Martier SS, Ager JW. The T-ACE questions: practical prenatal detection of risk-drinking. Am J Obstet Gynecol. 1989;160(4):863–70. https://doi.org/10.1016/0002-9378(89)90302-5.
22. Chang G, Wilkins-Haug L, Berman S, Goetz MA. The TWEAK: application in a prenatal setting. J Stud Alcohol. 1999;60(3):306–9. https://doi.org/10.15288/jsa.1999.60.306.
23. Burns E, Gray R, Smith LA. Brief screening questionnaires to identify problem drinking during pregnancy: a systematic review. Addiction. 2010;105(4):601–14. https://doi.org/10.1111/j.1360-0443.2009.02842.x.
24. Chang G, Orav EJ, Jones JA, Buynitsky T, Gonzalez S, Wilkins-Haug L. Self-reported alcohol and drug use in pregnant young women: a pilot study of associated factors and identification. J Addict Med. 2011;5(3):221–6. https://doi.org/10.1097/ADM.0b013e318214360b.
25. Carroll JC, Reid AJ, Biringer A, et al. Effectiveness of the Antenatal Psychosocial Health Assessment (ALPHA) form in detecting psychosocial concerns: a randomized controlled trial. CMAJ. 2005;173(3):253–9. https://doi.org/10.1503/cmaj.1040610.
26. Martin PR, Arria AM, Fischer G, et al. Psychopharmacologic management of opioid-dependent women during pregnancy. Am J Addict. 2009;18(2):148–56. https://doi.org/10.1080/10550490902772975.
27. Jones HE, Kaltenbach K. Treating women with substance use disorders during pregnancy: a comprehensive approach to caring for mother and child. New York, NY: Oxford University Press; 2013.
28. Briere J, Elliott DM, Harris K, Cotman A. Trauma symptom inventory. J Interpers Violence. 1995;10(4):387–401. https://doi.org/10.1177/088626095010004001.
29. Greenfield SF, Brooks AJ, Gordon SM, et al. Substance abuse treatment entry, retention, and outcome in women: a review of the literature. Drug Alcohol Depend. 2007;86(1):1–21. https://doi.org/10.1016/j.drugalcdep.2006.05.012.
30. Khan SS, Secades-Villa R, Okuda M, et al. Gender differences in cannabis use disorders: results from the National Epidemiologic Survey of Alcohol and Related Conditions. Drug Alcohol Depend. 2013;130(1–3):101–8. https://doi.org/10.1016/J.DRUGALCDEP.2012.10.015.
31. Forray A. Substance use during pregnancy. F1000Res. 2016;5. https://doi.org/10.12688/f1000research.7645.1.
32. Jones HE, Svikis D, Rosado J, Tuten M, Kulstad JL. What if they do not want treatment?: lessons learned from intervention studies of non-treatment-seeking, drug-using pregnant women. Am J Addict. 2004;13(4):342–57. https://doi.org/10.1080/10550490490483008.
33. Yonkers KA, Howell HB, Allen AE, Ball SA, Pantalon MV, Rounsaville BJ. A treatment for substance abusing pregnant women. Arch Womens Ment Health. 2009;12(4):221–7. https://doi.org/10.1007/s00737-009-0069-2.
34. Jones HE, Haug N, Silverman K, Stitzer M, Svikis D. The effectiveness of incentives in enhancing treatment attendance and drug abstinence in methadone-maintained pregnant women. Drug Alcohol Depend. 2001;61(3):297–306. https://doi.org/10.1016/S0376-8716(00)00152-6.
35. Abbott PJ, Weller SB, Delaney HD, Moore BA. Community reinforcement approach in the treatment of opiate addicts. Am J Drug Alcohol Abuse. 1998;24(1):17–30. https://doi.org/10.3109/00952999809001696.
36. Jones HE, O'Grady KE, Tuten M. Reinforcement-based treatment improves the maternal treatment and neonatal outcomes of pregnant patients enrolled in comprehensive care treatment. Am J Addict. 2011;20(3):196–204. https://doi.org/10.1111/j.1521-0391.2011.00119.x.
37. Mann K, Ackermann K, Croissant B, Mundle G, Nakovics H, Diehl A. Neuroimaging of gender differences in alcohol dependence: are women more vulnerable? Alcohol Clin Exp Res. 2005;29(5):896–901. https://doi.org/10.1097/01.ALC.0000164376.69978.6B.

38. Greenfield SF, Pettinati HM, O'Malley S, Randall PK, Randall CL. Gender differences in alcohol treatment: an analysis of outcome from the COMBINE Study. Alcohol Clin Exp Res. 2010;34(10):1803–12. https://doi.org/10.1111/j.1530-0277.2010.01267.x.
39. Handmaker NS, Miller WR, Manicke M. Findings of a pilot study of motivational interviewing with pregnant drinkers. J Stud Alcohol. 1999;60(2):285–7. https://doi.org/10.15288/jsa.1999.60.285.
40. Osterman RL, Dyehouse J. Effects of a motivational interviewing intervention to decrease prenatal alcohol use. West J Nurs Res. 2012;34(4):434–54. https://doi.org/10.1177/0193945911402523.
41. Perkins K, Scott J. Sex differences in long-term smoking cessation rates due to nicotine patch. Nicotine Tob Res. 2008;10(7):1245–50. https://doi.org/10.1080/14622200802097506.
42. Leventhal AM, Waters AJ, Boyd S, Moolchan ET, Lerman C, Pickworth WB. Gender differences in acute tobacco withdrawal: effects on subjective, cognitive, and physiological measures. Exp Clin Psychopharmacol. 2007;15(1):21–36. https://doi.org/10.1037/1064-1297.15.1.21.
43. Heckman CJ, Egleston BL, Hofmann MT, et al. Efficacy of motivational interviewing for smoking cessation: a systematic review and meta-analysis. Tob Control. 2010;19(5):410–6. https://doi.org/10.1136/tc.2009.033175.
44. Haug NA, Svikis DS, DiClemente C. Motivational enhancement therapy for nicotine dependence in methadone-maintained pregnant women. Psychol Addict Behav. 2004;18(3):289–92. https://doi.org/10.1037/0893-164X.18.3.289.
45. Tappin DM, Lumsden MA, Gilmour WH, et al. Randomised controlled trial of home based motivational interviewing by midwives to help pregnant smokers quit or cut down. BMJ. 2005;331(7513):373–7. https://doi.org/10.1136/bmj.331.7513.373.
46. Ierfino D, Mantzari E, Hirst J, Jones T, Aveyard P, Marteau TM. Financial incentives for smoking cessation in pregnancy: a single-arm intervention study assessing cessation and gaming. Addiction. 2015;110(4):680–8. https://doi.org/10.1111/add.12817.
47. Higgins ST, Bernstein IM, Washio Y, et al. Effects of smoking cessation with voucher-based contingency management on birth outcomes. Addiction. 2010;105(11):2023–30. https://doi.org/10.1111/j.1360-0443.2010.03073.x.
48. Turner E, Jones M, Vaz LR, Coleman T. Systematic review and meta-analysis to assess the safety of bupropion and varenicline in pregnancy. Nicotine Tob Res. 2018;21:1001. https://doi.org/10.1093/ntr/nty055.
49. Hoch E, Noack R, Henker J, et al. Efficacy of a targeted cognitive–behavioral treatment program for cannabis use disorders (CANDIS∗). Eur Neuropsychopharmacol. 2012;22(4):267–80. https://doi.org/10.1016/J.EURONEURO.2011.07.014.
50. Hoch E, Bühringer G, Pixa A, et al. CANDIS treatment program for cannabis use disorders: findings from a randomized multi-site translational trial. Drug Alcohol Depend. 2014;134:185–93. https://doi.org/10.1016/J.DRUGALCDEP.2013.09.028.
51. Jaques SC, Kingsbury A, Henshcke P, et al. Cannabis, the pregnant woman and her child: weeding out the myths. J Perinatol. 2014;34(6):417–24. https://doi.org/10.1038/jp.2013.180.
52. Terplan M, Ramanadhan S, Locke A, Longinaker N, Lui S. Psychosocial interventions for pregnant women in outpatient illicit drug treatment programs compared to other interventions. Cochrane Database Syst Rev. 2015;4:CD006037. https://doi.org/10.1002/14651858.CD006037.pub3.
53. Hull L, May J, Farrell-Moore D, Svikis DS. Treatment of cocaine abuse during pregnancy: translating research to clinical practice. Curr Psychiatry Rep. 2010;12(5):454–61. https://doi.org/10.1007/s11920-010-0138-2.
54. Schottenfeld RS, Moore B, Pantalon MV. Contingency management with community reinforcement approach or twelve-step facilitation drug counseling for cocaine dependent pregnant women or women with young children. Drug Alcohol Depend. 2011;118(1):48–55. https://doi.org/10.1016/J.DRUGALCDEP.2011.02.019.
55. Jones HE, Myers B, O'Grady KE, Gebhardt S, Theron GB, Wechsberg WM. Initial feasibility and acceptability of a comprehensive intervention for methamphetamine-using pregnant women in South Africa. Psychiatry J. 2014;2014:929767. https://doi.org/10.1155/2014/929767.

56. Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States. JAMA Psychiat. 2014;71(7):821. https://doi.org/10.1001/jamapsychiatry.2014.366.
57. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. In: Mattick RP, editor. Cochrane database of systematic reviews. Chichester, UK: John Wiley & Sons, Ltd; 2014. https://doi.org/10.1002/14651858.CD002207.pub4.
58. Swift RM, Dudley M, DePetrillo P, Camara P, Griffiths W. Altered methadone pharmacokinetics in pregnancy: implications for dosing. J Subst Abus. 1989;1(4):453–60. http://www.ncbi.nlm.nih.gov/pubmed/2485290. Accessed January 30, 2019.
59. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10(2):113–130.e22. https://doi.org/10.1016/J.JPAIN.2008.10.008.
60. Tracy TS, Venkataramanan R, Glover DD, Caritis SN. Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy. Am J Obstet Gynecol. 2005;192(2):633–9. https://doi.org/10.1016/J.AJOG.2004.08.030.
61. Substance Abuse and Mental Health Services Administration. Clinical guidance for treating pregnant and parenting women with opioid use disorder and their infants. Rockville, MD; 2018. https://store.samhsa.gov/product/Clinical-Guidance-for-Treating-Pregnant-and-Parenting-Women-With-Opioid-Use-Disorder-and-Their-Infants/SMA18-5054. Accessed January 30, 2019.
62. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med. 2010;363(24):2320–31. https://doi.org/10.1056/NEJMoa1005359.
63. Tran TH, Griffin BL, Stone RH, Vest KM, Todd TJ. Methadone, buprenorphine, and naltrexone for the treatment of opioid use disorder in pregnant women. Pharmacotherapy. 2017;37(7):824–39. https://doi.org/10.1002/phar.1958.
64. Ellis JD, Cairncross M, Struble CA, Carr MM, Ledgerwood DM, Lundahl LH. Correlates of treatment retention and opioid misuse among postpartum women in methadone treatment. J Addict Med. 2018;1:153. https://doi.org/10.1097/ADM.0000000000000467.
65. Schuckit MA. Treatment of opioid-use disorders. Longo DL, ed. N Engl J Med. 2016;375(4):357–68. https://doi.org/10.1056/NEJMra1604339.
66. Reece-Stremtan S, Marinelli KA. ABM clinical protocol #21: guidelines for breastfeeding and substance use or substance use disorder, revised 2015. Breastfeed Med. 2015;10(3):135–41. https://doi.org/10.1089/bfm.2015.9992.
67. O'Connor AB, Collett A, Alto WA, O'Brien LM. Breastfeeding rates and the relationship between breastfeeding and neonatal abstinence syndrome in women maintained on buprenorphine during pregnancy. J Midwifery Womens Health. 2013;58(4):383–8. https://doi.org/10.1111/jmwh.12009.
68. Welle-Strand GK, Skurtveit S, Jansson LM, Bakstad B, Bjarkø L, Ravndal E. Breastfeeding reduces the need for withdrawal treatment in opioid-exposed infants. Acta Paediatr. 2013;102(11):1060–6. https://doi.org/10.1111/apa.12378.

LGBTQIA: Lesbian, Gay, Bisexual, Transgender, Queer or Questioning, Intersex, Asexual or Allied

17

James Sherer and Petros Levounis

High-Yield Review Points

- Use warmth and curiosity to create an open and respectful dialogue with your patients about substance use and sexual orientation.
- Use of "party drugs" such as crystal methamphetamine, ecstasy, GHB, and ketamine is higher in many LGBTQIA populations but disproportionately so among gay men, whereas alcohol use is disproportionately higher among bisexual and lesbian women but lower among gay men.
- LGBTQIA people may use psychoactive substances to relieve increased stress stemming from discrimination and internalized homophobia or to enhance sexual pleasure during sex.

Introduction

Understanding, appreciating, and celebrating the lives of LGBTQIA people (lesbian, gay, bisexual, transgender, queer or questioning, intersex, asexual or LGBT for short) and the cultures of their communities helps mental health and addiction treatment practitioners provide optimal care for their patients. Part of understanding and treating LGBT people effectively is recognizing the higher rates of substance use in this group. In the LGBT population, 20–30% struggle with addiction, compared with approximately 17% of the general population [1, 2]. Higher rates of SUD can be understood in the light of the many challenges that the LGBT community faces daily, including stigma, marginalization, and shame, rather than placing blame on the community.

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While many underserved communities face similar problems, some challenges are unique to LGBT communities. LGBT people face a disproportionate amount of shame from family and friends due to discrimination, stigma, abuse, threats, hate crimes, public humiliation, and quite frequently internalized homophobia. In the face of these conditions, drugs, alcohol, and other addictions may offer an alternative for many in the LGBT community.

In many ways, substance use among LGBT people may be a way to avoid symptoms or ameliorate psychiatric conditions such as generalized anxiety disorder, major depressive disorder, eating disorders, and other disorders (or subclinical problems) that occur in the context of widespread stigmatization. While the need for general psychiatric care is increased in this population, many healthcare providers feel uncomfortable or even outwardly hostile toward this population, thus limiting their access to healthcare. To make matters worse, many members of the LGBT community have learned to distrust a traditionally homophobic and inhospitable healthcare system and may not seek help even when it is needed. As a result of this cycle, mental health deteriorates, and suicide rates in the LGBT community are high [1].

Many well-meaning and otherwise supportive health providers feel uncomfortable when meeting an LGBT patient for the first time due to a general lack of knowledge about the community and the terminology used to discuss and describe its members. In an attempt to avoid incorrect language usage, not asking about sexual orientation and gender may inadvertently alienate patients and compromise their care.

This section will define some of the terms that one should know to appropriately engage with LGBT patients. As mentioned above, LGBT refers to people who identify as lesbian, gay, bisexual, transgender, intersex, queer or questioning, intersex, and asexual. Many of these terms are not mutually exclusive. For example, most transgender people continue to use terms such as lesbian, gay, bisexual, etc. based on their sexual orientation. The term LGBT is meant to encompass a wide variety of people whose gender identity, gender expression, biological sex, and sexual orientation are outside the realm of heteronormativity.

Gender and sexual orientation are separate concepts. The former is mostly contained within an individual, while the latter refers to how the individual relates sexually with others. Gender is further understood as gender identity, gender expression, and biological sex. Similarly, sexually orientation is further understood as sexual orientation identity, sexual behavior, and sexual attraction. These are essential elements of our humanity and have distinct meanings [3]. Table 17.1 summarizes these concepts.

Most of these terms are not binary and can be best appreciated along a spectrum. Firstly, gender identity refers to how a person conceives of themselves, in their own minds, with regard to their gender role. The spectrum of gender identity goes from "man-ness" on one end to nongendered in the center to "woman-ness" on the other end. Next, there's gender expression, which is fundamentally different from gender identity. Whereas gender identity refers to one's inner conception of their gender, gender expression is an outward portrayal of gender. On the spectrum of gender expression, there is "feminine" on one side, androgynous in the center, and

Table 17.1 Gender and sexual orientation

Sexual orientation	Gender
Identity Examples: gay, lesbian, bisexual, straight, asexual, queer	*Identity* Examples: woman, gender fluid, man
Behavior Examples: same-sex partners, opposite-sex partners, both, neither	*Expression* Examples: feminine, androgynous, masculine
Attraction Kinsey scale 0, 1, 2, 3, 4, 5, 6, X	*Biological sex* Examples: female, intersex, male

"masculine" on the other side. Gender expression can encompass dress, affectation, and other outward signifiers of gender. Biological sex is assigned at birth and refers to the objectively measurable organs, hormones, and chromosomes that one possesses. Biological sex, while mostly binary with "female" and "male" genetic makeups, also includes intersex people, including those with rare genetic conditions such as androgen insensitivity syndrome and congenital adrenal hyperplasia.

Sexual orientation contains many concepts. Sexual identity is how one chooses to describe themselves with terms such as "straight," "gay," "lesbian," and so on. Sexual behavior may or may not be tied to sexual identity and refers to the sexual encounters that one is choosing to partake in. These encounters can be with same-sex partners, opposite-sex partners, neither, or both. Lastly, there is sexual attraction. This refers to whether one prefers sex with or is attracted to men, women, or both. Various scales of attraction have been proposed, but perhaps the most commonly cited is the Kinsey scale, which describes attraction in terms of gradations of orientation rather than simply "straight" or "gay." This scale runs from 0, meaning exclusively heterosexual, to 6, meaning exclusively homosexual. A person who falls on a 3 on the Kinsey scale is equally attracted to both the same and opposite genders. The scale also includes an X, which denotes those who indicate that they have no sexual encounters.

Table 17.2 provides a list of helpful and commonly used terms to describe those in the LGBT community. This list and definitions were agreed upon by the authors at the LGBT Resource Center at UC Davis [4].

General Approach to the LGBTQIA Patient

Health providers who have not treated many openly LGBTQIA people may have a certain level of trepidation when first approaching their patients. LGBT patients face stigma daily. In general, the best way to approach LGBT patients is with a sense of acceptance and a nonjudgmental attitude, much like any other patient. Creating a welcoming environment without judgment is a top priority. Simple things that heteronormative providers take for granted are often fraught subjects for those in the LGBT community, such as public restrooms and equal protections in the workplace. Patients may hide certain struggles that they are facing unless

Table 17.2 Glossary

Bisexual	A person whose primary sexual orientation is toward people of the same and other genders or toward people regardless of their gender
Cisgender	A gender identity, or performance in a gender role, that society deems to match the person's assigned sex at birth
Gay	A sexual orientation toward people of the same gender
Gender expression	How one expresses oneself in terms of dress and/or behaviors; it may be described as "masculine," "feminine," or "androgynous"
Gender identity	Sense of one's self as woman, man, trans, or some other identity, which may or may not correspond with the sex and gender that one is assigned at birth
Gender queer	A person whose gender identity and/or gender expression falls outside of the dominant societal norm for their assigned sex
Heteronormativity	A set of lifestyle norms, practices, and institutions that assume heterosexuality as a fundamental and natural norm
Homosexual/homosexuality	An outdated term to describe a sexual orientation in which a person feels physically and emotionally attracted to people of the same gender
Intersex	The experience of naturally developing primary or secondary sex characteristics that do not fit neatly into society's definitions of male or female
Lesbian	A woman whose primary sexual and affectional orientation is toward people of the same gender
MSM	An abbreviation for men who have sex with men; they may or may not identify as gay
Orientation	One's attraction or nonattraction to other people; it may be fluid or consistent and can change throughout the course of one's life
Pronouns	Linguistic tools used to refer to someone in the third person; examples are they/them/theirs, ze/hir/hirs, she/her/hers, he/him/his
Queer	A historical epithet used against people whose gender and/or sexuality does not conform to dominant expectations; some people have reclaimed the word
Sex	A medically constructed categorization; sex is often assigned based on the appearance of the genitalia, either via ultrasound or at birth
Straight	A word commonly used to describe a heterosexual male or female
Trans man	A chosen identifier of someone who was assigned female sex at birth choosing to live as a man; some trans men may also use the term FTM or F2M for "female to male"
Trans woman	A chosen identifier of someone who was assigned male sex at birth choosing to live as a woman; some trans women may also use MTF or M2F for "male to female"
Transgender	Adjective used most often as an umbrella term and frequently abbreviated to "trans"; this adjective describes a wide range of identities, including the two terms above
Transsexual (TS)	A person who lives full time in a gender different than their assigned birth sex and gender; many pursue hormones and/or surgery but not all

the provider is genuinely open and accepting. In the same vein, providers may want to differentiate between the real and imagined risks that LGTB patients face. For example, a commonly circulated myth among more conservative news outlets is that same-sex parents face unique challenges when it comes to raising children, and the children of LGBT adults experience higher incidences of mental illness [5]. This supposition is false, yet the narrative continues to be circulated [6]. Meanwhile, there are risks that disproportionately effect LGBT people. For example, the risk of HIV and HCV in LGBT populations who misuse substances has been shown to be relatively higher than those of their heteronormative counterparts [7]. Knowing these risks can guide the clinical interview and ensure patient safety.

While a practitioner may not know which pronoun a patient prefers to go by, or where exactly they fit in the broad and rich tapestry that makes up the LGBT community, almost any blunders that a practitioner may commit can be forgiven by patients so long as a current of curiosity and acceptance flows through the encounter.

The following example shows how even a provider who makes an incorrect assumption about the patient can be "excused" and very effective as long as warmth and curiosity are at the forefront of one's approach.

- *Provider: Hello Mr. Elbe, my name is Dr. Masters, and I'd like to discuss the process of the initial intake and what you can expect as we continue to work together.*
- *Patient: Hello Dr. Masters. I appreciate that, but I'd like you to know that I am in the process of transitioning and would prefer it if you refer to me as Ms. Elbe from now on.*
- *Provider: My sincere apologies Ms. Elbe, I'll make a note and be sure to do so going forward. While we are on the subject, which pronouns do you use? I use "he" and "him."*
- *Patient: It's not a problem. I use the pronouns "she" and "her." I appreciate that you asked me.*
- *Provider: Thank you. If you feel comfortable, I'd like to ask where you are in terms of your transition. I ask this because certain patients making the transition are on medications, such as hormones, that may interact with certain medications I prescribe.*
- *Patient: I have begun seeing an endocrinologist but have not begun taking any medications yet.*
- *Provider: Thank you. Let's return to the initial intake…*

Taking a Sexual History

Taking a sexual history as it relates to addiction is often overlooked when establishing care with an LGBT patient. The following are a few takeaway points to ensure that a sexual history is obtained in a respectful manner:

1. Avoid assumptions of heteronormativity. As appropriate, consider terms such as married, divorced, or widowed.
2. Remind yourself that marriage and monogamy are not synonymous.
3. Ask whether the patient prefers sex with men, women, both, or neither, regardless of the patient's gender identity.
4. Ask about sexual health and relationship styles in an open and accepting manner that avoids shame for the patient.
5. After building a respectful foundation of understanding, inquire as to sobriety during sex and which drugs the patient may use during sex.
6. Ensure that the patient's sexual encounters are consensual and that they are protected from sexual violence. If there is doubt in this regard, preface questions by saying that the provider has a duty to ensure safety, as well as maintain confidentiality.

- *Provider: I know from our earlier discussions that you use crystal methamphetamine weekly and that you mostly prefer sex with men. I'd like to ask if you ever use crystal meth right before or during sex.*
- *Patient: It's a little embarrassing to admit but yeah, especially in clubs, it's just the way things work. And the sex is much better, honestly.*
- *Provider: You told me that you try to use condoms when possible. When you are high on crystal, do you use a condom?*
- *Patient: Honestly, not really. I know I should, but it just doesn't always happen that way.*
- *Provider: So, while crystal meth is good for sex, it also might expose you to HIV and other diseases. I'd like to discuss those risks, so that you can make the most informed decisions going forward.*

Epidemiology of Substance Use in LGBTQIA Populations

Not only are LGBT adults more likely to use illicit substances, but also they use those substances more frequently than their heteronormative counterparts [2]. Whereas 17% of the general population used illicit substances in 2014, 39% of those in the LGBT population used illicit substances in the same year [2]. Cocaine, heroin, hallucinogens, inhalants, methamphetamines, and prescription drug misuse are higher in the LGBT population [2, 8–14]. The biggest discrepancies appear to occur with cocaine, hallucinogens (including ecstasy), inhalants, and methamphetamines, where use among gay men is at least three times that of their heteronormative counterparts [2, 8–14]. These increased rates of drug use cross the boundaries of sex and age within the LGBT community [7]. The increased use of these substances is perhaps linked to unique societal pressures faced by the LGBT population.

It follows that more people in the LGBT community need treatment for substance use problems than their heteronormative counterparts [2]. In 2015, 1.7 million LGBT adults needed substance use treatment, about 16% of the community as a whole, compared with 8% of the general population [2]. Of the 1.7 million who required treatment, only 340,000 received it [2]. Compared with the general

population, those in the LGBT community are actually somewhat more likely to seek and receive treatment for substance use [2]. However, there is still much to be done to ensure that those in underserved communities can access the substance use treatments they need.

Gay Men

Gay men are only slightly more likely to use tobacco products than their heteronormative counterparts (5% versus 4% prevalence) overall [8]. Men who report only having sex with men are far less likely to develop alcohol use disorders as compared with men who report only having sex with women [9]. While the numbers vary based on age and ethnicity, the general trend appears to hold true globally [9]. This is counterintuitive, considering that worldwide it is more socially acceptable for men to consume alcohol than for women [9]. However, gay men who do develop alcohol use disorders find it more difficult to quit. Relapse rates regarding alcohol are higher in gay men than lesbian or bisexual women in the same socioeconomic groups [9].

When discussing gay men, one must also discuss a class of substances of abuse that some refer to as "party drugs." Party drugs include crystal methamphetamine, methylene-dioxy-methamphetamine (MDMA) (ecstasy), gamma-hydroxy-butyrate (GHB), and ketamine (special K). While these substances are found throughout the general population, their use within a gay subculture is substantially higher than within other populations discussed in this chapter. Party drugs can enhance pleasure during sex and are routinely used by young gay men who "party and play," a code phrase for using drugs (party) and having sex (play) [10–13].

Crystal methamphetamine has affected the gay population disproportionately [10]. The drug may be referred to as "crystal," "Tina" (crystal becomes Christina, which then becomes Tina), or simply "meth." It can be snorted, smoked, or injected. Many studies have documented the rise of amphetamine use in gay populations across the United States [11, 15]. Initially, crystal methamphetamine was thought to be largely confined to clubs and used only occasionally to enhance pleasure during intercourse. However, one study showed that 78% of crystal methamphetamine users in the MSM population in New York City met criteria for dependence. Furthermore, even those who use the drug sporadically are at higher risk for sexually transmitted diseases such as HIV [10].

Ecstasy use has reached rates as high as 34% past-month use in some MSM populations, with over half of MSM populations reporting use at some point in their lifetime [11]. An analog of methamphetamine, ecstasy is psychoactive and can increase energy, empathy, and pleasure. It is also known as "X" or "scooby snacks" and typically comes in brightly colored, small, and therefore easy to swallow tablets.

While not as prevalent in the gay population overall, GHB and ketamine use among MSM who go to clubs is fairly high [13]. GHB may be referred to as "liquid X" or "liquid ecstasy" and is a central nervous system depressant that may lead to euphoria, increased sex drive, and tranquility [16]. It is available as an odorless, colorless drug that may be combined with alcohol. Similarly, ketamine may come in a powdered or liquid form and may be consumed in drinks, snorted, or injected.

Unlike GHB, when it is dissolved in drinks, it imparts a salty and distinct taste. Its effects and use as a "party drug" are similar to those of GHB. However, the two drugs, GHB and ketamine, are very different in terms of their lethality. GHB has a very narrow therapeutic window (dose range to achieve clinical effect), with the dose that will result in a desirable high being only modestly lower than a lethal dose, resulting in a very significant risk of respiratory collapse and death. It is more difficult to overdose on ketamine since it has a very wide therapeutic window.

Lesbians

Lesbian women are more likely to start smoking earlier and continue to use tobacco at higher rates than heterosexuals throughout adult life [8]. Furthermore, tobacco use disorder rates are higher regardless of the type of tobacco used. Every tobacco delivery method, from cigarettes (21% prevalence) to e-cigarettes (12% prevalence), hookahs (10% prevalence), and cigars (7% prevalence) are used more among lesbians than their heteronormative counterparts [8].

As with tobacco, alcohol plays a large social role in the lesbian community. Lesbians are more than three times as likely to develop alcohol use disorders compared with their heteronormative counterparts [9]. Lesbians are also more likely to report negative social and financial consequences due to alcohol use [9]. However, both lesbian and heterosexual women in recovery find it easier to abstain—or are more successful in abstaining—from alcohol as women have fewer relapses overall compared to men [9].

Lesbians have higher lifetime rates of ecstasy, cocaine, methamphetamine, and lysergic acid diethylamide (LSD) use compared with heterosexual women. Forty-nine percent of lesbian or bisexual women report using ecstasy at least once in their lifetime compared with 40% of age-matched heterosexual women [14]. The same applies for ketamine (19% versus 15%), GHB (9% versus 7%), and cocaine (47% versus 37%) [14]. More statistically relevant differences are seen with methamphetamine use (17% versus 9%) and LSD (33% versus 23%) [14]. When compared with substance use among gay men, lesbians have a more pronounced "age gap" with younger lesbian and bisexual women being much more likely to experiment with illicit substances compared with their older counterparts [14].

Review Questions

1. Alex, a 29-year-old male with a self-reported history of anxiety and depression, comes to you, a physician, for help. As the initial interview progresses, Alex asks you to use the pronouns "she" and "her" when referring to her. Later, she tells you that her partner, Pat, a woman, occasionally encourages her to use methamphetamine during sex. A little embarrassed, you realize you have been referring to Pat as "he." Alex is now somewhat upset. You've made an erroneous assumption about
   A. Gender identity
   B. Gender expression

C. Biological sex
D. Attraction
E. Affectation

Correct answer: D. Attraction

Gender identity, gender expression, and biological sex are the three dimensions of gender. Gender identity refers to how one conceives of themselves with regard to "man-ness" or "woman-ness." Gender expression refers to how one displays femininity or masculinity to the outside world. Biological sex refers to the sex that someone is assigned at birth. Sexual orientation is independent of the previous three factors and refers to the type(s) of person(s) that one relates to sexually. Identity, behavior, and attraction are the three elements that describe sexual orientation.

In the vignette, the physician assumed heteronormativity, thinking that a patient whose gender identity leans toward "woman-ness" must be attracted to men. Furthermore, you may have thought to yourself, perhaps unconsciously, that transgender women (Alex, for example) must be heterosexual or would have been happy staying with their gender assigned at birth (male for Alex). This is not true.

2. Bob, a 24-year-old man, comes to you for help. He identifies as "straight" but reluctantly admits having sexual experiences with other men "once in a blue moon." Last night, he was at a club, used a "party drug," saying "sorry, doc, all I could think of was that this guy looked just like Dwayne Johnson—how could I possibly remember the name of the drug?" and is now worried about any lasting effects that the mystery drug may have. He says, "The drug was already mixed into my Cosmo when the Rock look-alike—swear to god, doc, he looked just like the dude in the movies—handed it to me; he told me it would be fun." Bob answers your question that last night's drink did not taste any differently than the usual Cosmos he has at home with Barbara, and afterward he felt "incredibly relaxed, sexed up, and sexy." Which of the following substances the patient most likely ingested?
   A. Methylene-dioxy-methamphetamine (MDMA or "ecstasy")
   B. Gamma-hydroxy-methamphetamine (GHB)
   C. Lysergic acid diethylamide (LSD)
   D. Ketamine
   E. Delta-9-tetra-hydro-cannabinol (THC)

   Correct answer: B. GHB

   GHB may be referred to as "liquid X" or "liquid ecstasy" and is a central nervous system depressant that leads to euphoria, increased sex drive, and tranquility. It is available as an odorless, colorless drug that is frequently combined with alcohol. Similarly, ketamine or "special K" may come in a powdered or liquid form and may be consumed in drinks, snorted, or injected. However, ketamine has a more pungent taste and smell that some users describe as "salty." Both could lead to the effects described by the patient, but only GHB is odorless. GHB is far more likely than ketamine to result in LSD overdose and death.

   LSD would have had more potent hallucinogenic effects. Ecstasy is a sensual rather than sexual drug and is most commonly taken as a pill. Cannabinoids such as THC and cannabidiol (CBD) are typically smoked or consumed with food.

3. Helen, a 23-year-old woman, comes to you for help. When taking a sexual history, she tells you that she is a lesbian and has only had intercourse with other women. She says that it is difficult to meet other women in her rural town. "Traveling long distances to the state capital is the only way I can find other people like me." She later admits to using various substances to help her relax and meet people. Since high school, she has sporadically used cannabis, GHB, ketamine. She currently drinks about three beers a day. Which one of the following substances disproportionately affect women having sex with women (WSW) but not men having sex with men (MSM)?
   A. Cannabis
   B. GHB
   C. Alcohol
   D. Ketamine
   E. Hallucinogen

   Correct answer: C. Alcohol

   Whereas certain studies show that alcohol use disorder is less common in the MSM population compared with heterosexual men, alcoholism may be as much as three times more prevalent in lesbians and bisexual women as compared with heterosexual women. Cannabis, GHB, and ketamine use is higher in both lesbian and gay populations (but some studies show that they are relatively less prevalent in the lesbian population). While alcohol use disproportionately affects lesbians, it has also been shown that lesbian and bisexual women who enter treatment have higher rates of abstinence and fewer relapses compared with men.

References

1. National Academy of Medicine. The health of lesbian, gay, bisexual, and transgender people: building a foundation for better understanding. Washington, D.C.: The National Academies of Press; 2011.
2. Medley G, Lipari RN, Bose J, Cribb DS, Kroutil LA, McHenry G. Sexual orientation and estimates of adult substance use and mental health: results from the 2015 National Survey of Drug Use and Health. 2016; https://www.samhsa.gov/data/sites/default/files/NSDUH-SexualOrientation-2015/NSDUH-SexualOrientation-2015/NSDUH-SexualOrientation-2015.htm. Accessed 25 Nov 2018.
3. Killermann S. Breaking through the binary: gender explained using continuums; http://itspronouncedmetrosexual.com/2011/11/breaking-through-the-binary-gender-explained-using-continuums/. Accessed 25 Nov 2018.
4. The Regents of the University of California, Davis Campus. LGBTQIA Resource Center Glossary; https://lgbtqia.ucdavis.edu/educated/glossary. Accessed 25 Nov 2018.
5. Miller S. Three years after same-sex marriage ruling, protections for LGBT families undermined. USA Today. 2018; https://www.usatoday.com/story/news/nation/2018/06/04/same-sex-marriage-ruling-undermined-gay-parents/650112002/. Accessed 25 Nov 2018.
6. Thrasher SW. For gay and lesbian parents, equality is a myth when it comes to custody cases. The Guardian. 2014; https://www.theguardian.com/australia-news/2017/oct/23/children-raised-by-same-sex-parents-do-as-well-as-their-peers-study-shows. Accessed 25 Nov 2018.
7. https://www.hhs.gov/hepatitis/blog/2017/07/21/getting-in-sync-on-hiv-hep-c-and-lgbt-health.html.

8. Johnson SE, Holder-Hayes E, Tessman GK, King BA, Alexander T, Zhao X. Tobacco product use among sexual minority adults: findings from the 2012-2013 National Adult Tobacco Survey. Am J Prev Med. 2016;50(4):e91–e100.
9. Hughes TL, Wilsnack SC, Kantor LW. The influence of gender and sexual orientation on alcohol use and alcohol-related problems: toward a global perspective. Alcohol Res. 2016;38(1):121–32.
10. Halkitis PN, Parsons JT, Stirratt MJ. A double epidemic: crystal methamphetamine drug use in relation to HIV transmission among gay men. J Homosex. 2001;41(2):17–35.
11. Halkitis PN, Pollock JA, Pappas MK, et al. Substance use in the MSM population of New York City during the era of HIV/AIDS. Subst Use Misuse. 2011;46(2-3):264–73.
12. Halkitis PN, Green KA, Carragher D. Methamphetamine use, sexual behavior, and HIV seroconversion. J Gay Lesbian Psychother. 2006;10(3–4):95–109.
13. Halkitis PN, Palamar JJ, Mukherjee PP. Poly-club drug use among gay and bisexual men: a longitudinal analysis. Drug Alcohol Depend. 2007;89(2–3):153–60.
14. Parsons JT, Kelly BC, Wells BE. Differences in club drug use between heterosexual and lesbian/bisexual females. Addict Behav. 2006;31(12):2344–9.
15. Lee S, Levounis P. Gamma Hydroxybutyrate: an ethnographic study of recreational use and abuse. J Psychoactive Drugs. 2008;40(3):245–53.
16. Levounis P, Ruggiero J. Outpatient management of crystal methamphetamine dependence among gay and bisexual men: how can it be done? Prim Psychiatry. 2006;13(2):75–80.

Underserved Populations

18

Theddeus Iheanacho, Ayana Jordan, and Charles Dike

High-Yield Review Points

- People experiencing homelessness have significantly higher rates of substance use disorders (SUD) and worse health and psychosocial outcomes related to substance use.
- Racial and ethnic minority communities are disproportionately affected by substance use. This is driven by lower treatment initiation and engagement, an overwhelming mistrust of the healthcare system, and vulnerabilities within the structural determinants of health.
- While more than half of arrestees and prison inmates have a SUD, treatment penetration for people involved with the legal system remains low.
- Structurally and culturally competent care by clinicians and providers can reduce disparities in SUD health outcomes.
- Improved care coordination across different agencies in the legal system can enhance linkage to care for individuals involved in the system who have SUDs.
- Integrating and adapting SUD care in nontraditional and community settings has potential to increase access to treatment for underserved populations.

Homelessness and Substance Use Disorder (SUD)

Substance use disorders (SUD) are, perhaps, the major health-related cause of homelessness in the United States. Data from waves 1 (2001–2002) and 2 (2004–2005) of the National Epidemiologic Survey on Alcohol and Related Conditions, show that alcohol use disorders and drug use disorders independently increased

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prospective risk for first-time homelessness, after adjustment for ecological variables [1]. Analysis of data from the National Comorbidity Survey Replication (NCSR) showed that one of the strongest independent risk factors for past homelessness was lifetime substance use disorder and Black race [2]. Another study on homelessness among United States military veterans found that the strongest risk factors for homelessness, other than extreme poverty, were SUD, especially alcohol and drug use disorders [2, 3]. Specifically, opioid use disorder (OUD) appears to significantly increase the risk of homelessness. A national study of Veteran Health Affairs (VHA) service users found the prevalence of homelessness among veterans with OUD to be 34.6 percent, 28.7 times that of veterans without OUD. This suggests that OUD is a major risk factor for homelessness, substantially greater than for homelessness associated with unspecified SUD among veterans [4]. Furthermore, for people who exit homelessness into permanent supported housing, drug use disorder raised the odds of eviction by about 150%, while those with AUD were 50% more likely to be evicted [5].

Epidemiology of SUD Among Homeless Individuals

The major epidemiological surveys in the United States related to drug and alcohol use, namely the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) and the National Survey on Drug Use and Health (NSDUH), do not include homeless individuals [6, 7]. The NESARC items do include questions on past-year and lifetime homelessness. Consequently, available data on prevalence and correlates of SUD among people experiencing homelessness come from epidemiological studies of subgroups of homeless populations and homeless research focused on cities, states, or the Veteran Affairs (VA) healthcare system.

Alcohol use disorder In a study of homeless women (n = 780) seeking primary care services at Health Care for the Homeless clinics across 11 sites in the US, 19% reported a past-year AUD. Another study among sheltered homeless adults found that 17% of women (n = 211) and 26% of men (n = 370) were diagnosed with AUD. These rates are significantly higher than the rates of AUD for women and men in the general population based on NESARC data (women = 10%, n = 20,447, and men = 18%, n = 15,862). In a national study of homeless veterans admitted to the VA-supported housing program (n = 29,143), 16.6% had an AUD [8]. A study of homeless street youth in three US cities, Los Angeles, California, Austin, Texas, and St. Louis, Missouri (n = 146), found that 46.3% met the criteria for AUD [9].

Opioid use disorder Data on the prevalence of OUD among homeless adults are limited. A national study of homeless veterans receiving services in the VA healthcare system in 2012 (n = 191,391) showed that almost 18% had a diagnosis of OUD [4]. A survey of homeless-experienced persons engaged in primary care at five federally funded programs in the United States (n = 601) showed that 7.5% had used

illicit opioids in the 3 months prior to the survey [10]. In a study of patients presenting to an urban hospital emergency department with questions about housing, substance use, and other health and social factors among patients who did or did not report current literal (streets/shelter) homelessness, patients who were currently homeless (n = 316, 13.7%) versus nonhomeless (n = 1993, 86.3%) had higher rates of past-year heroin use (16.7% vs. 3.8%) and prescription opioid use (12.5% vs. 4.4%) [11]. These findings, although somewhat limited, indicate that OUD rate among homeless adults could be 15–20 times the 1% prevalence rate of opioid use disorder in the general adult US population [12].

Nicotine use disorder In a nationally representative cross-sectional survey of homeless and nonhomeless individuals using federally funded community health centers in 2009,individuals with a history of homelessness had a substantially higher prevalence of current smoking than never homeless people (57.3 versus 26.7%), while 74% of respondents with a history of homelessness were ever smokers, compared with 43.5% among those without a history of homelessness. These rates are almost four times the national average and in keeping with other studies of smoking among homeless adults in the United States [13].

Comorbidities and Mortality

By far, the most prevalent infections among homeless adults in the United States are hepatitis C virus (HCV), with rates ranging from 9.8% to 52.5%, and human immunodeficiency virus (HIV), with rates of 6.4–40%, and a SUD is a common primary risk factor for HCV and HIV infections. Additionally, unsafe sexual practices, prior incarceration, chronic psychiatric disorders, and history of intimate partner violence (for women), all of which are related to SUD, were also associated with a heightened risk of HCV and HIV infection [4, 14].

Homeless adults are more likely to die of overdose and have poorer health and social outcomes compared with matched cohorts in the general population [15]. One study of homeless adults in Boston showed that opioid overdose accounted for over 80% of drug-overdose-related deaths among homeless adults [16].

Barriers to Treatment

Although there is a great need for SUD services among the homeless, many homeless individuals do not use or receive these services. Only about 25% of homeless adults with SUD who are seeking treatment receive it. The most frequently cited barriers to treatment relate to insurance coverage, high copayments for services, lack of safe housing and place to stay to begin treatment, difficulty in accessing information about programs, not having personal contacts that could facilitate getting services, and maintaining contact with providers. At individual levels,

frequently cited reasons by homeless adults for not accessing treatment include their own denial, the shame and guilt of relapsing, and not knowing how to stop even when they have decided to do so. For homeless women, particular barriers to treatment are having a child who is a minor and chronic homelessness and having "a more street-based social network" [17]. For these reasons, compared with domiciled adults with SUD, homeless adults with SUD are less likely to initiate care, less likely to follow up with treatment, and less likely to access inpatient care [18]. This leads to poorer treatment outcomes.

Utilizing Existing Service Frameworks

With the high prevalence, morbidity, and mortality burden of SUD and the treatment gap that exist for the homeless populations, innovative, tailored, effective, sustainable, and acceptable approaches are needed to increase their utilization of SUD treatment. One approach is using the integrated care model [19] to include SUD treatment in the care package for the homeless by leveraging existing service frameworks and available resources, including peer support and counseling, medications for addiction treatment (MAT), and mobile services. In fact, the National Healthcare for the Homeless Council specifically recommends "flexibility," "tailored treatment," and bringing "treatment to places where homeless people are, including shelters" [20]. Clinical case management programs for homeless adults anchored in community health centers, short-term housing agencies, and traditional shelters provide housing support, employment, and social services [21]. This is an example of a sustained and robust framework of screening, assessment, monitoring, and connection to treatment with a potential for integrating specific SUD treatment modalities.

Treatment Interventions That Improve Outcomes for the Homeless Population

Over the past decade, "Housing first" models have shown a promise in reducing the burden of homelessness [22], and homeless services should screen for, identify, and provide access to care for substance use disorders and common comorbid conditions among their service users. Mobile treatment units offering "on-demand," flexible, and accessible MAT for opioid use disorder with medical and case management services is an example of a patient-centered approach to care delivery that can increase SUD treatment utilization among the homeless population. A program in New Jersey sought to reduce barriers to treatment by providing free, opioid agonist treatment (OAT) (methadone or buprenorphine) via mobile medication units (MMUs). The MMUs enrolled a greater proportion of homeless individuals than the fixed-site methadone clinics [23]. Earlier examples include the "methadone bus" project in Amsterdam [24] and the "mobile medical van" in New Haven [25].

Substance Use Disorders in Racial and Ethnic Groups

Overview of Racial and Ethnic Disparities in Addiction

The overall prevalence of mental health conditions is similar across racial and ethnic groups in the United States. However, there continues to be a disproportionate burden of illness experienced among underrepresented minority (URM) populations [26]. The following sections summarize the major take-home points of the existing racial and ethnic disparities in addiction, specifically those related to treatment and health outcomes for SUD.

Tobacco In a recent study, there was no difference found in cigarette smoking prevalence by race and ethnicity [27]. This differs from previous reports [28], where American Indians/Alaskan Natives (AIs/ANs) and Whites were found to use tobacco more than other URM groups. Blacks and Hispanics are less likely to be daily smokers, use smokeless tobacco or e-cigarettes, and had more reports of past-year quit attempts and higher use of menthol cigarettes compared with Whites. Interestingly, more Blacks were found to engage in smoking cessation treatment on the inpatient setting as compared with Whites, who were less likely to be interested in cessation services during treatment [29]. This highlights the importance of culturally informed care based on different racial preferences.

Alcohol Prevalence rates of alcohol use are higher among Whites, compared with URM populations, including Blacks, Hispanics/Latinos, AIs/ANs, Native Hawaiians/Pacific Islanders (NHs/PIs), and Asians [30]. However, Blacks and Hispanics/Latinos have more adverse health consequences as a result of their alcohol use [31]. In particular, Hispanics/Latinos are overrepresented in DUI-related fatalities [31], and AIs/ANs have the greatest self-reported rates of DUIs. Further, Blacks and Hispanics/Latinos are more likely to be involved in the legal system as a result of their alcohol use compared with Whites [32]. This underscores the need for more advocacy at the local, state, and national levels to address biased policies that inherently result in the overrepresentation of Blacks and Hispanics/Latinos with AUDs in the legal system, as opposed to obtaining substance use treatment.

Cocaine Blacks are more likely to use cocaine compared with Whites, and Blacks and Hispanics/Latinos have been shown to have higher rates of cocaine-related overdose deaths, compared with Whites [33] but less likely to engage in treatment and more likely to be involved in the legal system as a result of their substance use [34]. A clearer understanding of the factors that underlie these health disparities is crucial in preventing further drug-related overdose deaths in URM populations.

Cannabis In general, nonmedical cannabis use has been decreasing among all racial and ethnic populations; however, the rate of decrease among these groups has not been uniform and is not adequately understood [35]. For example, among adolescents in tenth grade, Black youth were more likely to show an increase in cannabis

use compared with Whites. Yet all racial ethnic groups in the 12th grade, except non-Hispanics/Latino Whites, demonstrate a linear increase in the prevalence of cannabis across time [35]. Data from the National Survey on Drug Use and Health from 2003 to 2015 [36] revealed that among adult cannabis users, the odds of cannabis abuse and dependence were greater among Blacks, AIs/ANs, and Hispanics/Latinos compared with Whites. These URM groups are less likely to initiate substance use treatment compared with Whites despite higher cannabis use [36].

Opioids Misuse of opioids is the largest drug epidemic in the history of the US, affecting all racial groups [34]. Whites have been most adversely impacted by the use of opioids, experiencing the most dramatic increase in opioid-related deaths [34]. However, AIs/ANs continue to have one of the highest rates of opioid-related deaths, with Blacks seeing a doubling of deaths since 2000, likely from heroin use [37]. Despite these increased death rates in AIs/ANs and Blacks, these URM groups have been largely left out of the greater sociopolitical discourse, with Blacks and Hispanics/Latinos in particular being far more likely to be arrested for their opioid use rather than provided treatment [34].

Reasons Accounting for These Disparities

The exact reasons accounting for racial and ethnic disparities in addiction are not well understood. However, there have been several theories cited for lower treatment engagement among URM populations, including societal and cultural stigma associated with accessing substance use treatment, mistrust of the medical system due to historic maltreatment, lack of health care coverage, circuitous pathways to care, lower socioeconomic status, and the absence of culturally informed treatment options [38].

Furthermore, due to the interpersonal nature of medicine, a clinician's assumptions about a patient based upon their race or ethnicity can indeed impact interactions with, the diagnosis of, and the implementation of a treatment plan for the patient [32]. Race, both that of the patient and the provider, can influence the care received, with several examples demonstrating substandard care of URM patients with SUD when compared with Whites [32]. We must therefore acknowledge that stereotypes of racial groups do indeed exist and can impact the perceptions, expectations, and interactions that a person may have with the health care system, particularly if they belong to or are assigned to a URM group [32]. Recently, there has been more discussions about the role of **implicit bias**, the subconscious association of a stereotypical attribute with a particular racial group [39], in the care of minority populations with SUD [40].

Another key concept in understanding the disparities that exist among racial and ethnic minorities must include an understanding of the conditions in which people live, learn, work, and play, collectively known as the ***social determinants of health*** (SDOH) [41], which can affect a wide range of health risks and outcomes. Unfortunately, racial and ethnic minorities are more likely to have poorer SDOH,

including higher unemployment rates, unstable housing, low income, unsafe neighborhoods, and substandard education [41]. Taken together, not having stable SDOH can contribute to worsened health outcomes from substance use [41] and further decrease the likelihood of URM populations to initiate, engage in, or complete substance use treatment [42].

Various Models of Care Hold Future Promise

There are many models of care being developed to address disparities in addiction among racial and ethnic minorities. Some examples of novel interventions that are culturally informed, meaning those that incorporate specific cultural norms into treatment considerations, that may prove useful can broadly be characterized as [1] integrated care models, [2] faith-based models, and [3] models that address the SDOH [43].

Integrated health models that provide comprehensive, multidisciplinary care are shown to be effective in the treatment of mental health disorders [44]. Primary care is often the entry point of care for many people, so colocalizing addiction treatment within primary care and utilizing peer recovery coaches (those with lived experience in SUD) or community resource workers may prove essential in addressing the complex needs of many URM populations. Further, the integration of cultural and linguistic preferences in care has also been shown to be effective in decreasing rates of attrition among URM populations [44]. An example of a cultural preference of care is the integration of faith into treatment models for addiction [45]. Given the importance and value of spirituality among many URM populations, the Substance Abuse and Mental Health Administration has specifically developed several faith-based programs to address substance use at the national, state, and local levels [45]. An example of a specific program that addresses SDOH includes the Center for Disease Control's Racial and Ethnic Approaches to Community Health (REACH), a national program geared at reducing racial and ethnic disparities in health, including tobacco use [43].

Substance Use Disorders and the Legal System

The link between substance use disorders (SUD) and legal problems is overwhelming and consistent. About half of federal and state inmates reported drug use in the month before their offense, and about half meet the criteria for a substance use disorder; in approximately 17% of all cases, illegal-drug-seeking behavior led to their crimes [46]. Also, about half of those with SUD had at least three prior sentences to probation or incarceration compared to a third of other inmates. In the juvenile population, half of adolescent boys and almost half of adolescent girls in juvenile detention had diagnosis of SUD [47].

Comorbid mental illness and SUD predominate in the offender population. Approximately 75% of state prisoners and local jail inmates who had a mental

health problem met the criteria for SUD [48]. Furthermore, probationers with co-occurring mental health and substance use disorders were significantly more likely to be at risk for future crimes than those with only one of SUD or mental illness [49].

For Blacks, the war on drugs firmly established the connection between SUDs and the criminal justice system (CJS); punishment rather than treatment was emphasized [50]. This led to a dramatic increase in the incarceration of Blacks, five to seven times higher than Whites in 2011, and to Blacks accounting for almost half of all prisoners incarcerated with a sentence of more than 1 year for a drug-related offense [51].

High numbers of people with SUD in the criminal justice system reflects, in part, the gap in treatment resources available in the community. For example, less than 12% of newly arrested individuals had been in outpatient or residential treatment for substance abuse in the preceding 12 months [52]. Research suggests that existing drug treatment programs have a capacity to serve only around 10% of offenders [53].

Potential Interventions at Various Stages of the Criminal Justice System

Treatment interventions can be delivered from the point of arrest, through courts, during preincarceration, during incarceration, and at reentry into the community.

Preincarceration interventions In many jurisdictions, the police have a wide latitude in interacting with offenders who appear to be under the influence of substances. They could, for example, divert the offender in lieu of arrest to the emergency room of an acute care hospital under statutes that allow them to transport persons whom the police assess as being a threat to themselves or others or gravely disabled due to mental illness or intoxication. In these cases, police jurisdiction and involvement end when the person is admitted to the ED. The police have more options when they work with mobile crisis teams (MCTs). MCTs facilitate diversion of patients into one of various substance use treatments on the condition that the person agrees to voluntarily enter or engage in the treatment.

Alternatively, individuals taken into custody by the police can be diverted post booking with a promise to appear on the condition that they seek treatment. Such diversion occurs under the direction of the court and is then evaluated by the court at arraignment. Court diversion staff, from the department of mental health or a similar agency assigned to the courts, advocate on behalf of patients and, following a court approval of diversion, facilitates transfer to an available treatment facility. Treatment occurs independent of the court, although the court monitors success in terms of compliance with the treatment programs and avoidance of arrest.

Drug courts (an example of so-called specialty courts), present in many jurisdictions but not in all states, work differently. They can assign criminal defendants and

offenders (adults and juveniles) who have alcohol and drug problems to community-based substance use treatment and rehabilitation services with monitoring and supervision by the court [54]. A major difference between court diversion under the auspices of departments of mental health and drug courts is the requirement by the latter that the individual plead guilty, usually of misdemeanor charges. With a successful completion of the program, the charges are usually expunged. In another example of a specialty court, offenders who have pled guilty to a felonious offense are sentenced for up to two years to a residential therapeutic community treatment system. The program, Drug Treatment Alternative to Prison (DTATP), significantly reduced recidivism and drug use and saved money over the cost of incarceration [55].

Preincarceration initiatives for managing SUD reflects the evolving recognition that punishment alone does not work for managing what is essentially a chronic brain disease. They are more effective at reducing recidivism and are significantly less expensive than incarceration in financial [56] and human costs [57]. There is less fracturing of family and neighborhood connections, which is important for African American communities, where many are under criminal justice control on any given day.

Treatment in jails (shorter term, local) or prisons (longer term, state or federal) Jails provide an important step in interrupting problematic substance use and beginning treatment. However, given the relatively short length of stay and rapid turnover, jails are more suited for the screening and identification of SUDs, the initiation of brief interventions, and referral to community treatment programs [58]. Research shows that participation in short-term SUD treatment program in jail decreased recidivism compared with a matched control group who did not participate in treatment [59]. According to SAMHSA, a majority of federal and state prisons provide substance use treatment, including detoxification, group or individual counseling, rehabilitation, and methadone or other pharmaceutical treatment [60]. However, only approximately a third of jails and juvenile facilities provide treatment. Despite these findings, however, the median percentage of offenders who had access to treatment (mostly drug education) at any given time was approximately 10% [60]. Of note, MAT in prison is markedly limited [61].

Postincarceration treatment The period immediately following release from incarceration is particularly dangerous for ex-prisoners. Former prisoners were 12.7 times more likely to experience drug-related deaths [62], especially in the 2 weeks following their release from prison, compared with the general population. Accidental drug overdose was the leading cause of death, followed by cardiovascular disease, homicide, and suicide. Other prominent causes of death included cancer, especially of lung and bronchus, and motor vehicle accidents, which are related to drug (including cigarette smoking) or alcohol use. Improved outcomes result from a connection with identified protective factors against adverse outcomes before or immediately following release from incarceration. These include structured SUD treatment programs, spirituality/religion, community-based resources (including self-help groups), and family [63].

The high rates of opioid overdose following release from incarceration [64] provides a rationale for urgent intervention with medication treatment with buprenorphine or methadone. In one study, prescription of MAT during incarceration and continuation on release from incarceration through coordination with outpatient services was associated with a 12.3% decrease in opioid-related overdose deaths compared with the preceding year [65].

For outpatient treatment to be successful, however, it is imperative that outpatient providers be comfortable working with patients with criminal history and that they work closely with former inmates to access housing, transportation, vocational training/employment, and other life skills.

Conclusion

Substance use disorders (SUD) are chronic, relapsing brain diseases associated with significant morbidity and mortality, especially for vulnerable and underserved populations, including the homeless, underrepresented minority populations, and those involved in the criminal justice system. Factors that increase the risk of SUD negative outcomes include poor socioeconomic status, impoverished environments, lack of or decreased access to medical and psychiatric care, challenges with housing and employment, personally mediated racism, and institutionalized racism. Individuals from disadvantaged, underrepresented minority populations and those involved in the criminal justice system are more likely to experience these barriers to recovery and to be exposed to the devastating consequences of addiction to substances. For treatments and interventions to be effective, they must address these issues in a coordinated and culturally and structurally relevant fashion.

Review Questions

1. Mr. Smith is a 56-year-old, employed, White male with history of diabetes, hypertension, and opioid use disorder. He lives in the rural areas of Ohio and recently became divorced from his wife of 20 years. Which of the following factors in Mr. Smith's history most likely puts him at risk for homelessness?
   A. Living in a rural area
   B. Being White
   C. Having a diagnosis of opioid use disorder
   D. Being recently divorced

   Answer is C.

   Explanation: Data show that a diagnosis of substance use disorder, especially opioid use disorder, is a strong risk factor for homelessness. Living in a rural area is in fact protective. Being Black is a risk factor for homelessness. Being divorced is not a known risk factor for homelessness.

2. Ms. Brown is a 45-year-old single, unemployed homeless female with history of substance use disorder, depression, and childhood sexual abuse. She drinks a pint of vodka daily and smokes crack cocaine a few times a week. Which of the following is a more likely comorbidity?
   A. Human papillomavirus
   B. Human immunodeficiency virus
   C. Hepatitis C
   D. Hepatitis A

   Answer is C.

   Explanation: Hepatitis C infection is the most common infection among homeless adults, with up to 52% prevalence rate; HIV is second, with up to 40% prevalence. No strong evidence suggests that HPV and hepatitis A viruses are highly prevalent among the homeless population.
3. A city-wide survey of adults living in a large metropolitan area in the United States found that most have used cannabis in the preceding year. Among adults 18 and older in the United States, which of the following racial or ethnic groups have the least odds of developing a cannabis use disorder?
   A. Blacks/African Americans
   B. American Indians/Alaskan Natives
   C. Non-Hispanics/Non-Latino Whites
   D. Hispanics/Latinos

   Answer is C.

   Explanation: Data from the National Survey on Drug Use and Health from 2003 to 2015 revealed that among adult (ages 18 and older) cannabis users, the odds of cannabis abuse and dependence were greater among Blacks, AIs/ANs, and Hispanics/Latinos compared with Whites. Unfortunately, these URM groups are less likely to initiate substance use treatment compared with Whites, despite higher rates of cannabis use disorder.
4. An anthropology researcher examining the impact of social determinants of health in the United States will find that which of the following factors have been shown to potentially reduce disparities among racial and ethnic minorities with SUD?
   A. Social and cultural stigma
   B. Racially concordant health providers
   C. Mistrust of the medical system
   D. Lack of healthcare coverage

   Answer is B.

   Explanation: For URM, having a provider of the same race is not implicated in health disparity and in fact can potentially enhance health outcomes for underrepresented minorities. There have been several theories cited for lower treatment engagement among URM populations, including societal and cultural stigma associated with accessing substance use treatment, mistrust of the medical system due to historic maltreatment, lack of health care coverage, circuitous

pathways to care, lower socioeconomic status, and the absence of culturally informed treatment options. In addition to these factors, the role of racism on various levels cannot be ignored.

5. During a court-ordered psychiatric evaluation of a jailed 22-year-old Black man awaiting trial on drug possession charges, the psychiatrist found one of the following to be correct regarding substance use in the criminal justice system:
   A. 90% of all inmates reported drug use in the month before their offense.
   B. Only 10% of adolescent boys in juvenile detention have a diagnosis of substance use disorder.
   C. Prisons are now aggressively treating identified inmates before their release back into the community.
   D. Drug courts, a specialty court that deals with criminal justice involving individuals with substance and alcohol use problems, are not available in all US states.

   Answer is D.

   Explanation: The Bureau of Justice statistics report that over half of all inmates reported drug use in the month before their offense. In the juvenile population, approximately half of adolescent boys in juvenile detention have a diagnosis of substance use disorder. Despite the recent escalation of deaths via opioid overdose, prescription of medication-assisted treatment for opioid use disorders is sorely lacking. Majority of prisons provide drug treatment in the form of detoxification, counseling, and rehabilitation.

   Drug courts, a specialty court that deals with criminal justice involving individuals with substance and alcohol abuse problems, are not available in all US states. In some states with drug courts, they are not uniformly distributed throughout the state; they are not available in all counties of the state.

6. A postdoctoral research fellow reviewing available data on substance use disorders among racial and ethnic groups in the legal system would find which of the following to be correct?
   A. The war on drugs targeted all racial and ethnic groups equally if cocaine was involved.
   B. Black and Hispanic offenders abused all drugs at rates higher than Whites.
   C. It is now more likely that substance abusing Blacks and Hispanic offenders will be committed to treatment in the community than to prison.
   D. Ready access to structured treatment programs, religious and self-help community groups, and family support have been shown to influence relapse and reoffending rates in Blacks

   Answer is D.

   Explanation: The war on drugs specifically targeted Blacks and led to a dramatic increase in incarceration of Blacks, five to seven times more than Whites. Whites abused opioids more than Blacks and Hispanics; substance-abusing Blacks and Hispanics are still more likely to be incarcerated than sent to treatment; structured treatment programs and the other supportive structures listed in answer d are protective factors against reoffending.

References

1. Thompson RG Jr, Wall MM, Greenstein E, Grant BF, Hasin DS. Substance-use disorders and poverty as prospective predictors of first-time homelessness in the United States. Am J Public Health. 2013;103(S2):S282–S8.
2. Greenberg GA, Rosenheck RA. Mental health correlates of past homelessness in the National Comorbidity Study Replication. J Health Care Poor Underserved. 2010;21(4):1234–49.
3. Tsai J, Rosenheck RA. Risk factors for homelessness among US veterans. Epidemiol Rev. 2015:mxu004.
4. Iheanacho T, Stefanovics E, Rosenheck R. Opioid use disorder and homelessness in the Veterans Health Administration: the challenge of multimorbidity. J Opioid Manag. 2018;14(3):171–82.
5. Montgomery AE, Cusack M, Szymkowiak D, Fargo J, O'Toole T. Factors contributing to eviction from permanent supportive housing: Lessons from HUD-VASH. Eval Program Plann. 2017;61:55–63.
6. Hasin DS, Grant BF. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) waves 1 and 2: review and summary of findings. Soc Psychiatry Psychiatr Epidemiol. 2015;50(11):1609–40.
7. Abuse S, Administration MHS. 2015 National survey on drug use and health. 2016.
8. Tsai J, Kasprow WJ, Rosenheck RA. Alcohol and drug use disorders among homeless veterans: prevalence and association with supported housing outcomes. Addict Behav. 2014;39(2):455–60.
9. Ferguson KM, Jun J, Bender K, Thompson S, Pollio D. A comparison of addiction and transience among street youth: Los Angeles, California, Austin, Texas, and St. Louis, Missouri. Community Ment Health J. 2010;46(3):296–307.
10. Stringfellow EJ, Kim TW, Gordon AJ, Pollio DE, Grucza RA, Austin EL, et al. Substance use among persons with homeless experience in primary care. Subst Abus. 2016;37(4):534–41.
11. Doran KM, Rahai N, McCormack RP, Milian J, Shelley D, Rotrosen J, et al. Substance use and homelessness among emergency department patients. Drug Alcohol Depend. 2018;188:328–33.
12. Saha TD, Kerridge BT, Goldstein RB, Chou SP, Zhang H, Jung J, et al. Nonmedical prescription opioid use and DSM-5 nonmedical prescription opioid use disorder in the United States. J Clin Psychiatry. 2016;77(6):772.
13. Baggett TP, Rigotti NA. Cigarette smoking and advice to quit in a national sample of homeless adults. Am J Prev Med. 2010;39(2):164–72.
14. Williams SP, Bryant KL. Sexually transmitted infection prevalence among homeless adults in the United States: a systematic literature review. Sex Transm Dis. 2018;45(7):494–504.
15. Lebrun-Harris LA, Baggett TP, Jenkins DM, Sripipatana A, Sharma R, Hayashi AS, et al. Health status and health care experiences among homeless patients in federally supported health centers: findings from the 2009 patient survey. Health Serv Res. 2013;48(3):992–1017.
16. Baggett TP, Hwang SW, O'Connell JJ, Porneala BC, Stringfellow EJ, Orav EJ, et al. Mortality among homeless adults in Boston: shifts in causes of death over a 15-year period. JAMA Intern Med. 2013;173(3):189–95.
17. Tucker JS, Wenzel SL, Golinelli D, Zhou A, Green HD Jr. Predictors of substance abuse treatment need and receipt among homeless women. J Subst Abus Treat. 2011;40(3):287–94.
18. Priester MA, Browne T, Iachini A, Clone S, DeHart D, Seay KD. Treatment access barriers and disparities among individuals with co-occurring mental health and substance use disorders: an integrative literature review. J Subst Abus Treat. 2016;61:47–59.
19. Shidhaye R, Lund C, Chisholm D. Closing the treatment gap for mental, neurological and substance use disorders by strengthening existing health care platforms: strategies for delivery and integration of evidence-based interventions. Int J Ment Heal Syst. 2015;9(1):40.
20. Matt Warfield BD. National Health Care for the Homeless Council. (May 2016). Medication assisted treatment: Buprenorphine in the HCH Community. 2016.

21. Winn JL, Shealy SE, Kropp GJ, Felkins-Dohm D, Gonzales-Nolas C, Francis E. Housing assistance and case management: improving access to substance use disorder treatment for homeless veterans. Psychol Serv. 2013;10(2):233.
22. Tsemberis S. Housing first: the pathways model to end homelessness for people with mental illness and addiction manual. Eur J Homeless. 2011;5(2):235–40
23. Hall G, Neighbors CJ, Iheoma J, Dauber S, Adams M, Culleton R, et al. Mobile opioid agonist treatment and public funding expands treatment for disenfranchised opioid-dependent individuals. J Subst Abus Treat. 2014;46(4):511–5.
24. Buning EC, van Brussel GH, van Santen G. The 'methadone by bus' project in Amsterdam. Br J Addict. 1990;85(10):1247–50.
25. Liebman J, Pat Lamberti M, Altice F. Effectiveness of a mobile medical van in providing screening services for STDs and HIV. Public Health Nurs. 2002;19(5):345–53.
26. Cook BL, Zuvekas SH, Chen J, Progovac A, Lincoln AK. Assessing the individual, neighborhood, and policy predictors of disparities in mental health care. Med Care Res Rev. 2017;74(4):404–30.
27. Pagano A, Gubner NR, Le T, Yip D, Williams D, Delucchi K, et al. Differences in tobacco use prevalence, behaviors, and cessation services by race/ethnicity: a survey of persons in addiction treatment. J Subst Abus Treat. 2018;94:9–17.
28. White HR, Nagin D, Replogle E, Stouthamer-Loeber M. Racial differences in trajectories of cigarette use. Drug Alcohol Depend. 2004;76(3):219–27.
29. Substance Abuse and Mental Health Services Administration. Results from the 2013 National Survey on drug use and health: summary of National Findings, NSDUH Series H-48, HHS Publication No. (SMA) 14–4863. Substance Abuse and Mental Health Services Administration: Rockville; 2014.
30. Keyes KM, Vo T, Wall MM, Caetano R, Suglia SF, Martins SS, et al. Racial/ethnic differences in use of alcohol, tobacco, and marijuana: is there a cross-over from adolescence to adulthood? Soc Sci Med. 2015;124:132–41.
31. Watt TT. The race/ethnic age crossover effect in drug use and heavy drinking. J Ethn Subst Abus. 2008;7(1):93–114.
32. Zapolski TCB, Pedersen SL, McCarthy DM, Smith GT. Less drinking, yet more problems: understanding African American drinking and related problems. Psychol Bull. 2014;140(1):188–223.
33. National Institute on Alcohol Abuse and Alcoholism (NIAAA) | Minority Health and Health Disparities [Internet]. [cited 2019 Apr 15]. Available from: https://www.niaaa.nih.gov/alcohol-health/special-populations-co-occurring-disorders/diversity-health-disparities.
34. Medlock MM, Shtasel D, Trinh N-HT, Williams DR, editors. Racism and psychiatry: contemporary issues and interventions [Internet]. Humana Press; 2019 [cited 2019 Apr 15]. (Current Clinical Psychiatry). Available from: https://www.springer.com/us/book/9783319901961.
35. Pacek LR, Malcolm RJ, Martins SS. Race/ethnicity differences between alcohol, marijuana, and co-occurring alcohol and marijuana use disorders and their association with public health and social problems using a national sample. Am J Addict. 2012;21(5):435–44.
36. James K, Jordan A. The opioid crisis in black communities. J Law Med Ethics. 2018;46(2):404–21.
37. Galea S, Rudenstine S, Vlahov D. Drug use, misuse, and the urban environment. Drug Alcohol Rev. 2005;24(2):127–36.
38. Keyes KM, Wall M, Feng T, Cerdá M, Hasin DS. Race/ethnicity and marijuana use in the United States: diminishing differences in the prevalence of use, 2006–2015. Drug Alcohol Depend. 2017;179:379–86.
39. Wu L-T, Zhu H, Swartz MS. Trends in cannabis use disorders among racial/ethnic population groups in the United States. Drug Alcohol Depend. 2016;165:181–90.
40. Hedegaard H, Warner M, Miniño AM. Drug overdose deaths in the United States, 1999–2015. NCHS data brief, no 273. Hyattsville: National Center for Health Statistics; 2017.
41. Acevedo A, Garnick DW, Lee MT, Horgan CM, Ritter G, Panas L, et al. Racial/ethnic differences in substance abuse treatment initiation and engagement. J Ethn Subst Abus. 2012;11(1):1–21.

42. Satcher D. Mental health: culture, race, and ethnicity—a supplement to mental health: a report of the surgeon general [Internet]. Washington, D.C.: U.S. Department of Health and Human Services; 2001 [cited 2019 Apr 15]. Available from: http://www.surgeongeneral.gov/library/mentalhealth/cre/.
43. Mojtabai R, Olfson M, Sampson NA, Jin R, Druss B, Wang PS, et al. Barriers to mental health treatment: results from the National Comorbidity Survey Replication (NCS-R). Psychol Med. 2011;41(8):1751–61.
44. LaVeist TA, Diala C, Jarrett NC. Minority health in America: findings and policy implications from the Commonwealth Fund minority health survey. Baltimore: Johns Hopkins University Press; 2000.
45. Garfield R, Damico A, Stephens J, Rouhani S. The coverage gap: uninsured poor adults in states that do not expand Medicaid–an update. Kaiser Family Foundation: Menlo Park; 2016.
46. Mumola CJ, Karberg JC. Drug use and dependence, state and federal prisoners, 2004. Bureau of justice statistics special report. 2006. Available at https://www.bjs.gov/content/pub/pdf/dudsfp04.pdf. Accessed on 14 April 2019.
47. Teplin LA, Abram KM, McClelland GM, Dulcan MK, Mericle AA. Psychiatric disorders in youth in Juvenile detention. Arch Gen Psychiatry. 2002;59(12):1133–43.
48. James DJ, Glaze LE. Mental health problems of prison and jail inmates. 2006. Available at https://www.bjs.gov/content/pub/pdf/mhppji.pdf. Accessed on 23 March 2019.
49. Balyakina E, Mann C, Ellison M, Sivernell R, Fulda KG, Sarai SK, Cardarelli R. Risk of future offense among probationers with co-occurring substance use and mental health disorders. Community Ment Health J. 2014;50:288–95.
50. Rosenberg A, Groves AK, Blankenship KM. Comparing black and white drug offenders: implications for racial disparities in criminal justice and reentry policy and programming. J Drug Issues. 2016;47(1):132–42.
51. Carson EA, Sabol WJ. Prisoners in 2011. U.S. Department of Justice: Bureau of Justice Statistics. Published December 2012. Available at http://www.bjs.gov/content/pub/pdf/p11.pdf. Accessed 12 Feb 2019.
52. Office of National Drug Control Policy. ADAM II: 2012 Annual report. Washington, DC: available at http://arc-associates.net/yahoo_site_admin/assets/docs/adam_ii_2012_annual_rpt_final_final.35175003.pdf. Accessed on 23 March 2019.
53. Taxman FS. Supervision—exploring the dimensions of effectiveness. Fed Probat. 2002;66:14–27.
54. Drug Courts. US Department of Justice, Office of Justice Programs. Available at https://www.ncjrs.gov/pdffiles1/nij/238527.pdf. Accessed on 23 March 2019.
55. Crossing the Bridge: an evaluation of the Drug Treatment Alternative-to-Prison (DTAP) Program. National Center on Addiction and Substance Abuse at Columbia University. 2003. https://www.centeronaddiction.org/addiction-research/reports/crossing-bridge-evaluation-drug-treatment-alternative-prison-dtap-program.
56. Zarkin GA, Cowell AJ, Hicks KA, Mills MJ, Belenko S, Dunlap LJ, Keyes V. Lifetime benefits and costs of diverting substance-abusing offenders from state prison. Crime Delinq. 2012;61:829–50.
57. McVay D, Schiraldi V, Ziedenberg J. Treatment or incarceration? National and state findings on the efficacy and cost savings of drug treatment versus imprisonment. Justice Policy Institute. 2004. Available at http://www.justicepolicy.org/uploads/justicepolicy/documents/04-01_rep_mdtreatmentorincarceration_ac-dp.pdf. Accessed on 14 April 2019.
58. Chandler RK, Fletcher BW, Volkow ND. Treating drug abuse and addiction in the criminal justice system: improving public health and safety. JAMA. 2009;301:183–90.
59. Bahr SJ, Harris PE, Strobell JH, Taylor BM. An evaluation of a short-term drug treatment for jail inmates. Int J Offender Ther Comp Criminol. 2013;57(10):1275–96.
60. Taxman FS, Perdoni ML, Harrison LD. Drug treatment services for adult offenders: the state of the state. J Subst Abus Treat. 2007;32(3):239–54.
61. Friedmann PD, Hoskinson R, Gordon M, Schwartz R, Kinlock T, Knight K, Flynn PM, Welsh WN, Stein LA, Sacks S, O'Connell DJ, Knudsen HK, Shafer MS, Hall E, Frisman LK. Mat Working Group of CJ-Dats. Medication-assisted treatment in criminal justice agencies affili-

ated with the criminal justice-drug abuse treatment studies (CJ-DATS): availability, barriers, and intentions. Subst Abus. 2012;33(1):9–18.
62. Binswanger IA, Stern MF, Deyo RA, Heagerty PJ, Cheadle A, Elmore JG, Koepsell TD. Release from prison-a high risk of death for former inmates. N Engl J Med. 2007;356(2):157–65.
63. Binswanger IA, Nowels C, Corsi KF, Glanz J, Long J, Booth RE, Steiner JF. Return to drug use and overdose after release from prison: a qualitative study of risk and protective factors. Addict Sci Clin Pract. 2012;7:3.
64. Merrall ELC, Kariminia A, Binswanger IA, Hobbs MS, Farrell M, Marsden J, Hutchinson SJ, Bird SM. Meta-analysis of drug-related deaths soon after release from prison. Addiction. 2010;105(9):1545–54.
65. Green TC, Clarke J, Brinkley-Rubeinstein L, Marshall BDL, Alexander-Scott N, Boss R, Rich JD. Postincarceration fatal overdoses after implementing medications for addiction treatment in a statewide correctional system. JAMA Psychiat. 2018;75(4):405–6.

Older Adults

19

Kavita Demla and Steven Huege

High-Yield Review Points

- As Baby Boomers retire, the proportion of older adults with substance use disorders has increased compared to earlier generations.
- The older adult population is less likely to be screened for substance use disorders and diagnoses may often be missed.
- Although not all seniors have serious medical problems, seniors who misuse substances generally face greater levels of medical comorbidity and functional impairment than their non-substance misusing peers.
- Physical illness and functional impairment can complicate addiction and the physical response to substances.
- Heavy and long-standing substance use has been shown to contribute to neurocognitive impairment.
- While many principles of addiction treatment remain constant across the age spectrum, good clinical care of the older adult requires an understanding of the aging process and how it alters the dynamics of treatment.

Introduction

Alcohol and drug use disorders are among the leading causes of disability worldwide. As the population of older adults increases, the magnitude of mental health and substance disorders will increase and the public health impact of these disorders will increase. Additionally, the prevalence of addiction among older adults is predicted to increase due to cohort changes. Notably, the "Baby Boom" generation is a

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group who were raised during the 1950s and 1960s and participated in the increased use of illicit drugs (e.g., heroin, cocaine), tobacco, and alcohol in the 1960s–1980s. This cohort is susceptible to both a history of and continued substance misuse, which will have physical and mental health consequences as it ages. However, relatively little research has been done examining the treatment and consequences of substance use disorders in older adults [1].

Substance use disorders are associated with social and health problems in seniors, including increased risk of hospitalization, nursing home placement, and death. Ninety percent of older adults use medications (both prescribed and over-the-counter) and many of these medications have potential adverse interactions with alcohol or illicit drugs. Additionally, older adults who are experiencing emotional and social issues such as bereavement, loneliness, and social isolation and medical problems such as chronic pain, insomnia, dementia, depression, or anxiety have an increased risk for substance misuse. These same problems may also be aggravated by substance use disorders [2].

However, substance use disorders in older adults are often not adequately diagnosed nor treated, as health professionals tend to overlook substance use disorders in the geriatric population, often attributing the symptoms to dementia, depression, or other problems instead. Additionally, older adults are more likely to hide their substance use problems and less likely to ask for help than younger adults. Although older adults respond well to age-specific, supportive and nonconfrontational group treatment targeted to their unique experience with substance use, only 7% of substance treatment centers reported having a program designed specifically for seniors in 2006 [2].

Demographics of Substance Use Disorders in Older Adults

The prevalence rates of substance use disorders have remained high among the Baby Boomers as they age, contrary to any generation preceding it. Substance use disorder rates among people older than 50 years old are expected to double from about 2.8 million in 2002–2006 to 5.7 million in 2020. This increase is expected for all gender, race/ethnicity, and age groups [2].

Prevalence of Substance Use Among Older Adults

Alcohol Although the geriatric population has increasing rates of illicit and prescription drug misuse, alcohol remains the most commonly used substance among older adults. Alcohol is also the most common substance involved in older adults seeking substance abuse treatment [3]. Therefore, much of the research studying substance use among older adults has centered on alcohol use disorders.

Data from the 2017 National Survey on Drug Use and Health (NSDUH) shows that the estimated 12-month prevalence in the general population for alcohol dependence or abuse as defined by the fourth edition of the *Diagnostic and Statistical*

Manual of Mental Disorders (DSM-IV) is 2.0% for adults aged 65 years and older. In this age group, the prevalence for binge alcohol use (defined by the use of 5 or more drinks for men or 4 or more drinks for women on the same occasion on at least 1 day in the past 30 days) is 11.5% and the prevalence for heavy use (defined as binge drinking on the same occasion on each of 5 or more days in the past 30 days) is 2.8% [4]. This data confirms findings from a study examining primary care clinics across the United States, in which a majority (22%) of older alcohol users were moderate drinkers (defined as 1–7 drinks per week), while episodes of binge drinking were common among all drinkers (24%), whether they were categorized as moderate, at-risk, or heavy drinkers. In this sample, it was found that frequent binge drinkers who were also heavy drinkers were more likely to report fair or poor health. These findings are of critical significance due to older adults' increased susceptibility to the toxic effects of alcohol and the potential interactions of binging, medications, and co-occurring illnesses [5].

Risk factors for alcohol misuse in late life include male gender, affluence, Caucasian race, and being young-old (in the early stages of late life). Therefore, having more financial resources and longer financial horizons is a predictor of increased drinking in older age [6]. Moreover, many older adults have chronic medical conditions associated with pain. Those older adults who have drinking problems report more severe pain, more disruption of functioning due to pain, and more use of alcohol to manage pain than older nonproblem drinkers. Hence, it is important to monitor the drinking behavior of older patients who have pain complaints, especially those who have preexisting problems with alcohol [7].

Illicit Drugs Older adults in the United States have one of the highest rates of illicit drug use compared to older adults in other countries [6]. The 2017 NSDUH data reveals that the 12-month prevalence rate of illicit drug use for adults age 65 years and older was 5.7%, while 0.2% of adults in this age group met criteria for past-year illicit drug dependence or abuse [4]. The Baby Boomer generation is unique as they have much higher rates of illicit drug use compared to their earlier cohorts, and they are a significantly larger group than previous cohorts. Baby Boomers, therefore, tend to have stark differences in attitudes toward recreational and illicit drugs compared to other generations.

Cannabis is the most prevalent drug after alcohol and tobacco used by adults 50 years and older in the United States and United Kingdom [2]. Although rates of illicit drug use among seniors have been relatively low historically, the prevalence of cannabis use among older adults is increasing in the United States. One study showed that the prevalence of past-year cannabis use among adults aged 50 years and older increased from 2.8% in 2006/2007 to 4.8% in 2012/2013, which was a 71% relative increase. Although those aged 65 years and older had a significantly lower prevalence of cannabis use compared to those aged 50–64 years old (1.4% vs. 7.1% in 2012/2013), adults aged 65 years and older had a much larger relative increase (250%) than adults aged 50–64 years (57.8%) [2].

This trend of increased cannabis use in the older adult population is not unanticipated, given the aforementioned high rates of substance use among Baby Boomers

compared to previous generations. Additionally, this is occurring in the setting of shifting attitudes and legalization and decriminalization of cannabis use in a growing number of states for recreational and medicinal purposes. As cannabis use increases, it will be important to examine the health consequences of its use in older adults, as little to no research has focused on this. Although studies are emerging regarding the benefits of cannabis for medicinal use, such as for chronic pain, the risks for older adults have not been well-defined. It is therefore important to screen patients of all ages for substance misuse and to consider the unique vulnerabilities of older adults to the physiological effects of legal and illegal substances.

Prescription, Nonprescription, and OTC Medication Use The United States is currently experiencing an opioid epidemic, with deaths from overdose of prescription opioids more than quadrupling between 1999 and 2015. Based on data from the 2015 National Survey on Drug Use and Health (NSDUH), older adults were shown to have had a higher 12-month prevalence of prescription opioid use than adults aged 18–49 years (39.5% vs. 35.7–37.0%) [8].

A 2006 study found that 25% of older adults use prescription medications that have abuse potential (e.g., opioids and benzodiazepines) [9]. These medications can cause some of the most serious problems for seniors who use them. Most of these drugs are obtained legally, and misuse is usually unintentional. Older adults with the following characteristics may be more likely to have problems with psychoactive medications: being female, being socially isolated, and having a history of substance misuse or mental health disorder. Additionally, long-term use of psychoactive medications, like benzodiazepines, is associated with cognitive deficits, confusion, falls, and depression in older adults. The rate of hospital admissions for drug-related conditions among older adults is increasing exponentially. Combining alcohol and psychoactive medications has even more potential for bad outcomes. Older adults experiencing pain, anxiety, or sleep disturbances are especially at risk for substance misuse [10].

Diagnosis and Screening of Substance Use Disorders in the Older Adult

The criteria for the formal diagnosis of substance use disorders as laid out by the *DSM-5* may be less relevant for older adults. In a study exploring age-related biases among the criteria for alcohol use disorders, findings revealed that older adults were half as likely as middle-aged adults to endorse the criteria related to tolerance, activities to obtain alcohol, social/interpersonal problems, and physically hazardous situations. Older adults were also less likely to endorse recurrent physical/psychological problems than younger cohorts [11].

These findings may be explained by the unique biologic and social factors present in late life. For example, older adults generally experience a reduction in tolerance to substances due to the age-associated physiologic changes that increase the effects of alcohol and other substances. This interferes with one of the criteria of substance use disorders: increased tolerance. Additionally, interference with social

or occupational areas of life or other consequences of substance use may be less likely to occur or less noticeable in old age due to a natural departure from these roles (i.e., through retirement or social isolation due to loss of peers). Furthermore, it may be that older adults blame the physical/psychological effects of alcohol on other areas in their life, such as the aging process itself, and in turn practitioners may be less likely to detect these issues as related to alcohol [6, 11].

As a result of these diagnostic issues, many who study substance use in the geriatric population deemphasize the reliance on *DSM* criteria to identify problematic substance use requiring treatment. They instead use a two-tier categorical classification: at risk and problem use. At-risk substance use refers to those who use substances above the recommended or prescribed levels but who experience few or no consequential physical, mental, emotional, or social problems. These individuals merit thorough screening and secondary prevention due to their high risk for developing such problems. Problem substance use, on the other hand, is characterized by those individuals who are already having problems in physical, mental, emotional, or social areas of life as a result of substance use. In contrast to at-risk substance users, identification of individuals with problem use does not depend on the quantity and frequency of use, but on the context in which substances are used. For example, older adults may have medical problems, such as gout or pancreatitis, even with minimal levels of alcohol consumption.

Older adults are less likely to be screened for substance use. Although awareness is increasing for the need for routine screening among older adults for substances, there are still several factors that inhibit adequate screening and identification of substance use disorders in older adults. For example, the potential stigma and discomfort related to the assessment of addiction and the similarities of substance use disorder with both symptoms of normal aging and other illnesses common in later life can impede detection of substance use disorders. Additionally, older adults often have difficulty identifying their own risky behavior regarding substance use, making the identification of this behavior by the clinician even more difficult.

Moreover, many older adults and even their family members may view alcohol use as being their "one last pleasure," which creates a complex picture of substance use in late life. When assessing older adults for substance use, it is important to remember that older adults respond more to a supportive, nonconfrontational approach and that they are more likely to be forthcoming about potentially stigmatizing behaviors if they think the clinician is genuinely interested in their overall health.

Screening tools for the geriatric population include the CAGE questionnaire, which has been extensively studied and validated for use in older adults, or the MAST-G, which is a tool that was specifically designed to identify drinking problems in the geriatric population by modifying the Michigan Alcohol Screening Test. The MAST-G is more relevant to alcohol use in later life as it focuses more on potential stressors and behaviors, rather than questions about family, vocational, and legal consequences of use. This tool is easy to administer, low cost, more specific than the CAGE in identifying problematic use, and useful to detect lifetime problematic use; however, it lacks information about frequency, quantity, and current problems.

The Alcohol Use Disorders Identification Test (AUDIT) is also validated in older adults to assess current alcohol problems. Additionally, the Comorbidity-Alcohol Risk Evaluation Tool (CARET) is useful for identifying older adults at risk of alcohol misuse as it assesses for quantity and frequency of alcohol consumption, presence of co-morbid diseases, high-risk behaviors, and concomitant use of medications that may interact adversely with alcohol. It too has shown validity with older adults and can detect a wider spectrum of hazardous use as it assesses criteria apart from just quantity and frequency of drinking that could present dangers more common in later life. The CARET is therefore more sensitive than the AUDIT and the MAST-G. Most older adults found to be at-risk drinkers by the CARET are identified as such due to their use of medications in combination with alcohol.

Physiology of Aging and Medical and Functional Complications of Substance Use for Geriatric Patients

Alcohol: As the percentage of lean body mass and total body water decreases with age, the ability of the liver to process alcohol is also decreased, while the permeability of the blood-brain barrier and neuronal receptor sensitivity to alcohol increase. As a result, older adults have higher blood alcohol concentrations and increased impairment than their younger counterparts in response to alcohol use at equivalent consumption levels. Older adults also have less awareness of their impairment, leading them to be more vulnerable to the effects of alcohol even in moderate amounts. Older at-risk drinkers are more likely to experience alcohol-related problems and functional impairment, such as impaired instrumental activities of daily living. This creates a unique and complicated picture of vulnerabilities for seniors, as they have increased rate of comorbid medical and psychiatric conditions. Even those older adults who had healthy drinking levels in young and middle age and then sustained these habits through older age may have increased risk for health problems [4]. The impact of alcohol use on the geriatric population has led the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to lower recommended drinking thresholds for adults 65 years and older [3].

Hazardous levels of drinking increase the risk of hypertension, diabetes, and other medical conditions in older adults. Alcohol misuse also significantly affects mood, sleep, and general health functioning. Depression in turn has been linked to relapses in drinking and increased alcohol intake. Low-risk drinkers, on the other hand, score better on general health, physical functioning, pain, mental health, and emotional functioning than both people who are hazardous drinkers and those who abstain from alcohol [10].

Some studies have shown that moderate alcohol consumption (no more than one standard drink per day) is associated with decreased morbidity and mortality among older adults. For example, older adult drinkers have been shown to have fewer falls, greater mobility, and improved physical functioning compared to

nondrinkers. Despite these findings, it is important to note that there may be trade-offs of moderate alcohol use for older adults. Moderate drinking may decrease the risk of ischemic stroke and increase the risk of hemorrhagic stroke, for example. Alcohol also has many potential interactions with medications. Therefore, it is essential to weigh the benefits of alcohol for older adults with each individual's unique context, including age, comorbid illnesses, gender, and genetics [6].

Medications, tobacco, and illicit drugs: The same physiological differences that render older adults more vulnerable to effects of alcohol compared to other age groups also render them more vulnerable to drug effects and interactions. For example, older adults have less lean muscle mass and more body fat. Therefore, benzodiazepines, which are fat-soluble, have a longer duration of action in older adults and can cause excessive sedation. Benzodiazepines with long half-lives in particular should be prescribed with caution. Additionally, older adults often see multiple providers, each of whom may prescribe medications that may interact with one other and/or with alcohol or other substances. Alcohol and cannabis, for example, increase the sedative effects of barbiturates, benzodiazepines, and opiates. Unintentional misuse may occur when older adults take more prescribed medications than intended, confuse pills, or borrow a medication from another person (e.g., use a dose of someone else's lorazepam or zolpidem for sleep).

Tobacco use in older adults is associated with several health consequences, including greater mortality, coronary events and cardiac deaths, cancer, COPD and pulmonary function decline, osteoporosis, hip fractures, loss of mobility, and poorer physical functioning. Tobacco also may decrease the efficacy of treatments for these conditions. It is not yet clear which of these health risks for tobacco use are also true for cannabis use [6].

Cannabis has been increasingly accepted both medicinally and recreationally. The risks of cannabis use have not been well-defined for older adults; however, these risks may be more pronounced in the geriatric population, especially those who have multiple chronic conditions. For example, cannabis causes increased heart rate, blood pressure, and respiratory rate and a quadruple increase in the risk for heart attack after the first hour of smoking it. These effects may increase the risk of cardiovascular events among older adults, particularly those who have preexisting disease. Smoking cannabis may lead to pulmonary illness and infection, to which older adults are more vulnerable. Cannabis has been tied to cerebrovascular events, for which, again, increasing age is a risk factor. Additionally, cannabis has acute effects on cognitive function and may have residual long-term effects, which is important to consider as older adults may already have compromised cognitive function [6, 12].

Studies show that the majority of older adult cannabis users perceive that there is either no risk or only a slight risk associated with cannabis use. However, one particular concern related to the geriatric population in particular is falls. Unintentional falls are common for older adults and are a major cause of morbidity and mortality, linked to functional decline and disability. Although alcohol use has been associated

with falls among older adults, no studies have yet examined the risk of falls among older adults who use cannabis. Additionally, it has been found that older adults who use cannabis are more likely to use other substances, including tobacco, alcohol, and/or illicit drugs, rendering them even more vulnerable to poor physical and mental health outcomes. Therefore, patients need to be educated about the risks of cannabis use and more research needs to be done to study how the effects of cannabis may ultimately impact the chronic diseases, geriatric conditions, and daily functioning of older adults [12].

Substance Use and Neurocognitive Disorders

It is well-established that alcohol use disorders in particular have neuropsychological consequences linked with permanent damage to the structure and function of the brain. However, there is debate regarding the classification of alcohol-related cognitive impairment. Currently, diagnostic systems identify two main syndromes of alcohol-associated cognitive disorders: alcohol-related dementia (ARD) and Wernicke–Korsakoff syndrome (WKS, an alcohol-induced persisting amnestic syndrome) [13].

Debate surrounding ARD and WKS involves the question of whether it is possible to have dementia directly resulting from ethanol neurotoxicity (a primary alcoholic dementia) or whether the dementia results from another underlying pathology (i.e., thiamine deficiency) or multiple factors (e.g., neurotoxicity in combination with nutritional deficiencies). Several confounding factors associated with the lifestyles of alcohol users have hindered the ability to clarify this distinction, including head injury, psychiatric and other substance abuse comorbidities, and a higher rate of vascular risk factors. Moreover, there has been little research into the prevalence of these comorbidities in the ARD population despite evidence that they are associated with the presence and maintenance of substance use disorders in both younger and older adults. The term "alcohol-related brain damage" is increasingly being used to encompass the heterogeneity in both etiology and clinical presentation of these disorders.

The relationship between the level of alcohol use and cognitive outcomes is complicated by varying definitions of drinking levels in the literature, which in part reflects the different definitions of a "standard drink" among different countries. Elements of drinking patterns (e.g., duration and severity of misuse, binge, and withdrawal periods) and difficulties getting an accurate self-report of past drinking also complicate attempts to establish the relationship between drinking levels and later cognitive impairment. Some studies suggest that individuals with ARD have had up to 60 years of drinking and up to 120 drinks per week at the heaviest, although the length and severity of drinking vary widely.

While heavy use increases the risk of dementia, there have been some studies that show that low to moderate drinking reduces the risk of dementia. This is thought to be due to the inhibitory effect of ethanol on platelet aggregation,

reduction of inflammatory markers, and alteration of serum lipids, which reduce the risk of coronary artery disease and ischemic stroke. On the other hand, heavier drinking may lead to adverse cerebrovascular changes (hypertension and increase triglycerides) and increased risk of arterial thrombosis, cardiac disorders, and strokes. Animal models have shown that low levels of alcohol protect cortical and hippocampal neurons against synapse damage induced by amyloid-β and α-synuclein, which may provide an explanation for the protection of alcohol against dementia syndrome.

Key characteristics differentiate alcohol-related cognitive disorders from neurodegenerative conditions, including stabilization or improvement in cognition with sobriety; cognitive deficits in executive, visuospatial, and memory domains with spared language function; and neurological symptoms such as ataxia. Neuroimaging may show atrophy in the mammillary bodies, thalamus, and cerebellum, and ventricular enlargement may be seen, though these findings vary.

Regarding potential reversibility of cognitive deficits, studies have shown individuals with alcohol use disorder had improvement on tests of nonverbal recall from short-term (working) and long-term memory, nonverbal immediate memory-attention, visuospatial abilities, and ataxia with abstinence. This may be significant for older adults as working memory is critical for many daily activities. Improved gait and balance may be particularly meaningful for physical well-being to reduce the risk of falls compounded with advancing age [14].

Treatment Considerations for the Older Adult

Opportunities to assess and refer older adults to substance use treatment are often overlooked. The geriatric population is more likely to receive referrals from non-healthcare settings (e.g., the criminal justice system, self-referral, or community social services providers) than from healthcare providers, even though many older adults in need of treatment present in healthcare settings due to other medical concerns. Older adults entering treatment for substance use disorders are more likely to be white, male, high school educated, widowed or divorced, retired, and disabled. This suggests a lack of a routine schedule associated with employment. In Sahker's analysis of individuals receiving substance use treatment in 2010–2013, up to 54% of older adults were living alone, and many widowed, suggesting a significant problem in social isolation and risk for adverse outcomes from many disorders in late life [15].

Many treatment options exist for older adults, depending on the setting and severity of problems; however, access to specialized services tailored for older adults is limited. In addition to potential biases leading to the under-detection of substance use disorders in the geriatric population, other barriers that older adults face when accessing specialized treatment include stigma and shame surrounding substance-related problems, geographic isolation, financial concerns, or transportation difficulties [6].

Brief interventions include using aspects of motivational interviewing (MI) or motivational enhancement therapy; however, rigorous controlled trials of older adults and MI have yet to be conducted. Nevertheless, the limited studies that have examined MI in older adults have supported the expectation that MI is as effective with older adults as it is with younger adults [16]. Other brief interventions include providing education, focusing on alcohol and prescription medication misuse, in the primary care setting. Normative feedback, in which the older adult's drinking is compared with his or her peers, is combined with brief advice, and seems to be an effective intervention for older adult drinkers.

Case and care management models, offered in primary care settings or community-based agencies, offer many advantages to the geriatric population. They provide a comprehensive approach, addressing the complexity of medical and psychiatric conditions common in the older population, and connect isolated older adults to community resources. The substance use interventions are also embedded in a broad approach addressing health, lessening stigma, and working toward a common goal among older adults: overall improved health. There is evidence that case management models are particularly effective at engaging and maintaining older at-risk drinkers in treatment.

As with younger populations, formal substance use treatment ranges from detoxication to outpatient treatment or aftercare. Both individual and group treatments are recommended for older adults to address their unique issues. It has been found that confrontational approaches are ill-suited for older adults, and indeed for any individual in whom the provider wishes to encourage substance use treatment. Supportive therapy models were specifically designed to focus on developing support and successful coping for older-adult substance misusers. This therapy focuses on building social support, improving self-esteem, and taking a global approach to treatment planning by addressing various biopsychosocial areas in the patient's life. There is also evidence for the effectiveness of CBT with older adults. As this therapy is highly structured and takes a didactic approach, it may be helpful to older adults with memory difficulties.

Alcoholic or Narcotic Anonymous and their related groups can be helpful for older adults, though some experts have recommended customizing meetings for this population by slowing the pace to adapt to cognitive changes that occur in aging and devoting attention to coping with loss and extending social support.

Regarding pharmacologic treatments, most of the research to date on older adults has been conducted on medications treating smoking cessation or alcohol use, including FDA-approved medications such as disulfuram, acamprosate, and naltrexone, while other medications, such as varenicline, are emerging. Evidence about the efficacy and safety for some of these medications is lacking for use in an older population, and as such, medications should be used with caution in this population. For example, disulfiram places extra strain on the cardiovascular system within older adults, and thus, may be contraindicated. Naltrexone is well-studied for use in older adults and has demonstrated some effectiveness with this population. The major limitation, however, is that many older adults have chronic pain, and naltrexone blocks the effect of opiate-based pain medications. Naltrexone can also potentiate preexisting depressive symptoms.

Review Questions

1. An 85-year-old African-American male presents to his PCP with complaints of chronic back pain secondary to sports injuries. He denies a prior history of substance use, but admits that he enjoys a cocktail several days a week at the exclusive country club at which he plays golf and is a member. Which of the following factors increase the risk of this patient misusing alcohol?
   A. Non-Caucasian race
   B. Old-old age status (>80 y/o)
   C. Affluence/financial resources
   D. Negative prior history of substance misuse
   E. Active lifestyle

   Answer: C: Affluence/financial resources

   Explanation: Risk factors for alcohol misuse in late life include male gender, affluence, Caucasian race, and being young-old (in the early stages of late life). Therefore, having more financial resources and longer financial horizons is a predictor of increased drinking in older age. Patients with a prior history of substance use and decreased activity due to pain/medical problems are also at higher risk of alcohol misuse.
2. A 71-year-old female presents to your office for concerns about concentration and memory. During the evaluation, you ask about substance use and learn that she smokes marijuana that her grandson gets from a medical marijuana dispensary every night "to sleep." What are the top three substances used by US adults 50 years and older?
   A. Alcohol, Benzodiazepines, Opiates
   B. Alcohol, Cannabis, Opiates
   C. Cannabis, Opiates, Tobacco
   D. Alcohol, Tobacco, Cannabis
   E. Cocaine, Alcohol, Opiates

   Answer D: Alcohol, Tobacco, Cannabis

   Explanation: Cannabis is the most prevalent drug after alcohol and tobacco used by adults 50 years and older in the United States and United Kingdom.
3. A 72-year-old female presents seeking treatment for alcohol misuse after her family stated that she needed to get help during an "intervention" in which her children and grandchildren participated. Which of the following criteria would she be less likely to endorse than a middle-aged or younger patient?
   A. Physical/Psychological Problems
   B. Social/Interpersonal Problems
   C. Tolerance
   D. Physically Dangerous Situations
   E. All of the above

   Answer E: All of the above

   Explanation: Due to various social and physical factors, older adults are less likely than their younger cohorts to report social and physical/psychological

problems, tolerance, and being in physically dangerous situations. Thus, it has been proposed that the *DSM* criteria to identify substance use disorders in the older adult are less applicable than they are for younger adults.

4. A 62-year-old male American Indian reports having little alcohol consumption in his youth, but since he retired 2 years ago, he feels bored and will often starting drinking at lunch time and consume 5–6 beers before he goes to bed at night. Older adults who consume alcohol are at greater risk of functional impairment and alcohol related problems due to which of the following physiological changes associated with aging?
   A. Decreased Permeability of Blood-brain Barrier
   B. Lowered Hepatic Metabolism of Alcohol
   C. Lowered Neuronal Receptor Sensitivity
   D. Increased Lean Mass
   E. Increased Total Body Water

   Answer B: Lowered Hepatic Metabolism of Alcohol

   Explanation: As the percentage of lean body mass and total body water *decrease* with age, the ability of the liver to process alcohol is also *decreased*, while the permeability of the blood-brain barrier and neuronal receptor sensitivity to alcohol *increase*.
5. A 79-year-old African-American female reports daily cannabis use since her late teenage years when she was a "groupie," following her favorite classic rock bands around the country. She cannot remember a period without using cannabis for more than a few days. Cannabis use in older adults has been linked with the following adverse effects?
   A. Frontotemporal Dementia
   B. Migraines
   C. Alzheimer's Dementia
   D. Cerebrovascular Events
   E. Parkinson's Disease

   Answer D: Cerebrovascular Events

   Explanation: Cannabis has been tied to cerebrovascular events. Although cannabis has acute effects on cognitive function and may have residual long-term effects, there is no current evidence linking cannabis use to the development of neurodegenerative disorders such as Parkinson's, FTD, or Alzheimer's, nor to development of migraines in older adults.

References

1. Oslin DW. Evidence-based treatment of geriatric substance abuse. Psychiatr Clin North Am. 2005;28(4):897–911, ix.
2. Han B, Gfroerer JC, Colliver JD, Penne MA. Substance use disorder among older adults in the United States in 2020. Addiction. 2009;104(1):88–96.
3. Han BH, Moore AA, Sherman S, Keyes KM, Palamar JJ. Demographic trends of binge alcohol use and alcohol use disorders among older adults in the United States, 2005-2014. Drug Alcohol Depend. 2017;170:198–207.

4. Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality. Results from the 2017 National Survey on drug use and health: detailed tables [internet]. Rockville: SAMHSA; 2017. [cited 2019 Jul 29]. Available from: https://www.samhsa.gov/data/report/2017-nsduh-detailed-tables.
5. Kirchner JE, Zubritsky C, Cody M, Coakley E, Chen H, Ware JH, et al. Alcohol consumption among older adults in primary care. J Gen Intern Med. 2007;22(1):92–7.
6. Kuerbis A, Sacco P, Blazer DG, Moore AA. Substance abuse among older adults. Clin Geriatr Med. 2014;30(3):629–54.
7. Brennan PL, Schutte KK, Moos RH. Pain and use of alcohol to manage pain: prevalence and 3-year outcomes among older problem and non-problem drinkers. Addiction. 2005;100(6):777–86.
8. Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription opioid use, misuse, and use disorders in U.S. adults: 2015 National survey on drug use and health. Ann Intern Med. 2017;167(5):293–301.
9. Simoni-Wastila L, Yang HK. Psychoactive drug abuse in older adults. Am J Geriatr Pharmacother. 2006;4(4):380–94.
10. Blow FC, Barry KL. Alcohol and substance misuse in older adults. Curr Psychiatry Rep. 2012;14(4):310–9.
11. Kuerbis AN, Hagman BT, Sacco P. Functioning of alcohol use disorders criteria among middle-aged and older adults: implications for DSM-5. Subst Use Misuse. 2013;48(4):309–22.
12. Han BH, Sherman S, Mauro PM, Martins SS, Rotenberg J, Palamar JJ. Demographic trends among older cannabis users in the United States, 2006-13. Addiction. 2017;112(3):516–25.
13. Ridley NJ, Draper B, Withall A. Alcohol-related dementia: an update of the evidence. Alzheimers Res Ther. 2013;5(1):3.
14. Sullivan EV, Rosenbloom MJ, Lim KO, Pfefferbaum A. Longitudinal changes in cognition, gait, and balance in abstinent and relapsed alcoholic men: relationships to changes in brain structure. Neuropsychology. 2000;14(2):178–88.
15. Sahker E, Schultz SK, Arndt S. Treatment of substance use disorders in older adults: implications for care delivery. J Am Geriatr Soc. 2015;63(11):2317–23.
16. Serdarevic M, Lemke S. Motivational interviewing with the older adult. Int J Ment Health Promot. 2013;15(4):240–9.

Professionals

20

Jonathan C. Lee, P. Bradley Hall, and Penelope P. Ziegler

High-Yield Review Points

- Professionals in safety-sensitive positions have a responsibility to the public that should be considered when using substances and for substance use disorder treatment.
- Safety-sensitive workers with substance use disorders require intensive, multidisciplinary, multimodal treatment in a cohort of peers with continued monitoring.
- Certain safety-sensitive workers have direct access to drugs with addiction liability, increasing the risk for misuse and relapse.

Introduction

The lifetime prevalence of substance use disorders among physicians is approximately 10–12%, which is similar to the general population rate. In the general population, relapse rates are as high as 40–60% following treatment. However, physicians who receive addiction treatment with continuing care and monitoring by state physician health programs (PHPs) have abstinence rates as high as 78% over 11 years [1]. The prevalence of substance use and mental health concerns among American

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attorneys was studied in a sample of almost 13,000 licensed, employed attorneys who completed surveys assessing for alcohol use, drug use, and symptoms of depression, anxiety, and stress; 21% of participants screened positive for hazardous, harmful, and potentially alcohol-dependent drinking, which was at a rate higher than the general population [2]. This study highlighted the need for attorney-specific prevention and treatment interventions as well as resources for lawyer assistance programs (LAPs).

Professionals in safety-sensitive positions have a responsibility to the public. Safety-sensitive occupations are defined by the following three factors: the size of the population that they affect, the depth of the effects from potential impairment, and the amount of public trust that is implied in that worker's occupation. Examples of safety-sensitive workers include healthcare workers, airline pilots, attorneys and judges, and public servants in the police and fire areas. Safety-sensitive workers require intensive primary treatment, typically for a minimum of 30–90 days, and continued treatment and monitoring due to potential impact on the public welfare. Safety-sensitive workers do best when offered cohort-specific treatment. Certain safety-sensitive workers have direct access to addictive substances, which increases the risk of relapse [3].

Safety-sensitive workers are typically regulated by an entity to ensure safety to practice and to protect the public. Examples of regulatory agencies include licensing boards (e.g., state medical boards, boards of nursing, state bar associations for attorneys) and the Federal Aviation Administration (FAA) for pilots. Monitoring programs, such as physician health programs (PHPs), are often available as an alternative to regulatory boards. PHPs provide care management to monitor adherence to continuing care and recovery activities; alcohol and drug testing to verify complete abstinence from intoxicating substances; advocacy and support of safety-sensitive workers in recovery; and coordination with regulatory agencies if participants fail to adhere to recommendations.

Identification and Assessment

If a safety-sensitive worker is identified as having a possible substance use disorder, they should be referred for a diagnostic evaluation. Safety-sensitive workers may need to discontinue working during this initial evaluation phase because of potential public health risks. Assessment of co-occurring psychiatric and medical conditions is crucial as these other conditions can exacerbate substance use disorders and impact treatment planning. Evaluations should be conducted by licensed professional(s) who specialize in assessing safety-sensitive workers; evaluators may require approval by a regulatory entity, such as the medical board. These multidisciplinary, multimodal team evaluations include face-to-face interviews with the safety-sensitive worker; history and physical examination; mental status examination; often neurocognitive/neuropsychological testing, laboratory studies as indicated including a comprehensive urine drug screen, hair test, and phosphatidyl

ethanol (PEth) test; collateral contacts with referring entity, family members, supervisor(s), and others as indicated; completion of appropriate releases of information to obtain needed collateral and to allow transmission of the evaluation report to the necessary stakeholders.

Treatment

Treatment of safety-sensitive workers with severe substance use disorders may start in the residential or partial hospitalization program with full immersion into a therapeutic milieu with group and individual counseling and medication management [4]. The level of care can be adjusted based on case specifics, DSM-5 criteria, and the expectation of the regulatory and/or monitoring entity.

The treatment team should be trained in the specifics of safety-sensitive professionals' work environment that may impact their recovery. For example, access to controlled substances is common in the work environment for anesthesiologists, and this issue affects monitoring and prognosis because of the potential for relapse on substances that are available in the work setting. Staff seek to understand and address the potential occupational stressors and traumas (e.g., first responders finding patients who are injured/dead) related to safety-sensitive positions. Staff should be aware of the psychosocial context of addiction treatment in the patient's particular cohort. For example, healthcare providers commonly struggle with accepting the role of being a patient [3]. It is also important to consider the political context of licensure board perceptions of how behaviors, such as professional boundary violations, can result from untreated addiction.

Treatment is tailored to address common defenses and maladaptive coping skills. Staff need training to manage the dynamic defenses and coping mechanisms (e.g., intellectualization, denial, minimization) common in safety-sensitive professionals. Clinical staff (e.g., counselors, nurses, and others providing specific treatment) may need supervision to avoid reactive judgment, which may limit self-disclosure from safety-sensitive workers.

Safety-sensitive workers benefit from profession-specific group therapy that allows for self-disclosure and discussion on boundary transgressions related to substance use disorders and professional roles. The model of cohort-specific group therapy has been studied and supported by physician health programs [4]. Peers in recovery often are able to confront each other on behaviors that are part of the relapse process, which may lead to using addictive substances [5]. It is important to balance the need for privacy with the involvement of professional patients' family and workplace to support their recovery.

Profession-specific support groups, such as Caduceus for healthcare professionals or Birds of a Feather for pilots, can provide mentorship, sponsorship, and hope for professionals in recovery. Participation and involvement in mutual support groups (e.g., Alcoholics Anonymous, other 12-step groups, and Self-Management And Recovery Training groups) are essential parts of treatment and monitoring for professionals.

Effective treatment involves coordinating continuing care providers and monitoring entities to minimize risks for relapse during transitions in care and ensure long-term recovery support. Monitoring entities, such as physician health programs (PHPs), Human Intervention Motivation Study (HIMS) programs for commercial airline pilots, lawyer assistance programs (LAPs), typically expect complete abstinence from alcohol and intoxicating drugs for a duration of 1–5 years or more. Staff should be aware of specialty drug testing (e.g., ethyl glucuronide and ethyl sulfate from alcohol metabolism) utilized for evaluation, treatment, and monitoring of safety-sensitive professionals. Monitoring includes case management to observe participant behaviors, compliance with the treatment plan, involvement of the worksite, adherence to recovery activities (e.g., attendance of 12-step meetings), and biological testing (e.g., urine drug screening, breathalyzer, blood testing for biomarkers of alcohol metabolites, hair/nail drug screens).

Contingency management is a component of treatment and monitoring for safety-sensitive workers. Case managers interact with participants and provide feedback on the submission of requested data and identify emerging issues. Data collected (e.g., drug screen results, check-in reliability for drug screens, attendance at mutual support groups and therapy sessions, tracking of appropriately prescribed medications) affect the frequency of contact with participants and frequency of drug screens. Complex drug screening is often managed by a third-party administrator with medical review officer support and carefully reviewed by the monitoring program. Participants experience positive reinforcement when drug screens (including costs) decrease in frequency based on compliance with check-ins and periods of no detected substance use. When there is a concern for safety to practice, monitoring programs can utilize negative reinforcement by removing safety-sensitive workers from the workplace or fulfilling the required reporting of them to their respective regulatory agencies.

Medications for relapse prevention should be considered for safety-sensitive workers. Due to regulations of various monitoring and licensure entities, there may be medications that are not considered appropriate due to concern for impacting the ability of the professional to practice with reasonable skill and safety. Extended release naltrexone, as opposed to agonist treatment, may be the preferred medication-assisted treatment for a healthcare professional with opioid use disorder due to return to work requirements enforced by a specific state medical board or monitoring program.

Return to Work Considerations

It is important to assess cognitive abilities of safety-sensitive workers. In some cases, neuropsychological testing may be required to determine safety to return to work recommendations. Occupational, licensing, and legal issues need to be addressed prior to the professional receiving permission to return to work in a staged and graduated manner. Work triggers or cues should be identified and be part of the relapse prevention plan. The work environment needs to make

appropriate accommodations to encourage adherence to the continuing care contract with monitoring (i.e., alcohol/drug screening and case management) by a designated entity to provide accountability [6]. Supervising personnel need to be trained in addressing profession-specific return to work issues for recovering safety-sensitive workers.

Conclusion

The combination of intensive, multidisciplinary, multimodal treatment in a cohort of peers followed by continuing care, long-term contingency management with monitoring and participation in mutual support groups is considered the gold standard for addiction treatment in safety-sensitive workers to sustain long-term recovery [4, 7, 8].

Review Questions

Bob is a 62-year-old OB/GYN physician whose medical license has been suspended due to caring for patients while intoxicated with alcohol on numerous occasions. No adverse medical outcomes were noted. He completed a residential addiction treatment program. He was recommended to continue care in an intensive outpatient program and participate in monitoring with a state physician health program. Which of the following is a component of physician health programs (PHPs)?

A. Addiction treatment programs
B. Care management to monitor adherence to continuing care and recovery activities
C. Liver and metabolic panel testing
D. Diagnosis and treatment of physicians with substance use disorders
E. Exclusion of the state medical licensing board if participant fails to adhere to recommendations

Correct Answer: B

Explanation: Physician health programs (PHPs) are not addiction treatment programs, nor do they directly provide such treatment [4]. PHPs do provide care management, advocacy and support of physicians, and drug and urine test monitoring. PHPs may report to the state medical licensing boards if participants fail to adhere to the treatment plan.

References

1. DuPont RL, McLellan AT, Carr G, Gendel M, Skipper GE. How are addicted physicians treated? A national survey of physician health programs. J Subst Abus Treat. 2009;37:1–7.
2. Krill PR, Johnson R, Albert L. The prevalence of substance use and other mental health concerns among American attorneys. J Addict Med. 2016;10(1):46–52.

3. Earley PH. Special populations: persons in safety sensitive occupations. In: Mee-Lee D, Shulman GD, Fishman MJ, Gastfriend DR, Miller MM, Provence SM, editors. The ASAM criteria. 3rd ed. Carson City: The Change Companies; 2013.
4. DuPont RL, McLellan AT, White WL, Merlo LJ, Gold MS. Setting the standard for recovery: physicians' health programs. J Subst Abus Treat. 2009;32(2):159–71.
5. Angers DH, Talbott GD, Bettinardi-Angres K. Healing the healer: the addicted physician. Madison: Psychological Press; 1998.
6. Earley PH. Physician health programs and addiction among physicians. In: Ries RK, Fiellin DA, Miller SC, Saitz R, editors. Principles of addiction treatment. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2009.
7. Body JW, Knight JR. Substance use disorders among physicians. In: Galanter M, Kleber HD, editors. Textbook of substance abuse treatment. 4th ed. Arlington: The American Psychiatric Publishing, Inc.; 2008.
8. Talbott GD, Wilson PO. Physicians and other health professionals. In: Lainson JH, Ruiz P, Millman RB, Langrod JG, editors. Substance abuse: a comprehensive textbook. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2005.

Part IV

Other Topics

Co-occurring Medical Disorders

21

Aaron Meyer

High-Yield Review Points

- Neurologic deficits from alcohol may range from mild cognitive impairment to development of Wernicke–Korsakoff syndrome. Alcohol consumption may lead to dilated cardiomyopathy, atrial fibrillation, and hypertension.
- Chronic benzodiazepine use can increase dementia risk. Tolerance also leads to drug-induced insomnia and alterations in sleep architecture.
- Cardiovascular risks from cocaine include coronary vasospasm, cerebrovascular accidents, and myocardial infarction.
- Amphetamine use is associated with development of hypertension and heart failure related to reduced ejection fracture.
- Opioid-induced hyperalgesia is a complication of long-term opioid use, and intravenous use has led to increased rates of HIV and Hepatitis C, cardiovascular consequences such as endocarditis, and thrombophlebitis and cellulitis.
- Individuals between the ages of 55 and 80 years who have >30 pack/year smoking history and have smoked within the past 15 years require an annual screening CT Chest to evaluate for lung cancer.

Physical complications from substance use have a profound impact on quality of life. These consequences have broad social and economic considerations including life expectancy, disability claims, and healthcare costs. Healthcare providers have a critical role in educating the public and their patients about the risks of developing substance use disorders and specific health consequences related to specific substances, including worse outcomes with common health conditions.

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Alcohol

Neurologic deficits may range from mild cognitive impairment to development of Wernicke–Korsakoff syndrome. Wernicke encephalopathy is an acute syndrome that is characterized by ataxia, ophthalmoplegia and confusion, and is caused by thiamine deficiency. Thiamine deficiency in alcohol use disorder is related to combination of inadequate dietary intake, decreased gastrointestinal absorption and storage. As thiamine metabolism increases with high glucose intake, clinicians must ensure that parenteral thiamine is administered prior to glucose infusion [1]. Imaging findings may consist of generalized cerebral atrophy and enlarged ventricles, similar to characteristics common in individuals with neurodegenerative processes [2].

Cardiovascular deficits with chronic use include both anatomic and electrical conduction abnormalities. Alcohol consumption may lead to dilated cardiomyopathy, atrial fibrillation, and hypertension [3]. Alcohol use is linearly correlated with increased risk of cerebrovascular accidents [4]. As alcohol impairs platelet aggregation and damages gastrointestinal mucosa, consumption has been linked to development of esophageal varices, gastric ulcerations, and pancreatitis. The liver can be affected with inflammation and steatohepatitis. A severe consequence of problematic use is alcoholic cirrhosis that sometimes requires transplantation [5]. An individual's transplant candidacy can depend on several factors, including duration of sobriety.

Laboratory abnormalities are common in patients with alcohol use disorder. Hepatic dysfunction can lead to hematologic abnormalities such as increased bilirubin, thrombocytopenia, and hypoalbuminemia [6]. Elevated transaminases (alanine transaminase (ALT) and aspartate transaminase (AST)) are common, and gamma-glutamyl transferase (GGT) is a sensitive marker of heavy alcohol use. However, GGT is not specific for alcohol use with elevated levels in patients with obesity, diabetes, and non-alcohol-related hepatic disorders. Similarly, carbohydrate-deficient transferrin is a serum marker of long-term, heavy alcohol use, correlating with previous 30 days of alcohol consumption. Phosphatidylethanol is an ethanol metabolite and used to detect longer-term exposure (up to 4 weeks) [7]. Severe alcohol use disorder is also linked to malnutrition and vitamin deficiencies such as low B12, folate, and thiamine. These vitamin deficiencies are related to histopathological findings of megaloblastic red blood cells (denoted by increased mean corpuscular volume on complete blood count) [8].

Sedative-Hypnotics

Benzodiazepine use has dramatically increased since the 1980s, and they are popularly prescribed as anxiolytics and for seizure prevention. While there are acute indications for this class of medications, there are significant deleterious effects with long-term use. Chronic benzodiazepine use is associated with an increase in all-cause mortality and elevated fall risk, specifically in geriatric populations. The increased fall risk is associated with a corresponding increase in fracture risk, notably hip fractures [9]. This can negatively impact mobility and lead to loss of functional independence. There is a concerning association with benzodiazepine

prescriptions and concurrent opioid prescriptions that can exacerbate the cognitive complications of sedative-hypnotic use. An often overlooked feature of chronic benzodiazepine use is an increased dementia risk [10]. Tolerance also leads to drug-induced insomnia and alterations in sleep architecture. Maternal-fetal complications may include slightly increased risk of cleft-lip and cleft-palate, particularly with diazepam, though the quality of the studies is low, along with neonatal respiratory depression and dependence [11]. Prescribers should be aware of the problems with abrupt discontinuation, which are similar to alcohol withdrawal, including seizures and withdrawal-related delirium.

Stimulants

Physical complications from stimulants can vary depending on the substance. Cardiovascular risks from cocaine include coronary vasospasm (from vasoconstriction), cerebrovascular accidents, and myocardial infarction [12]. Further, a significant emergency consequence from cocaine use is aortic dissection and possible rupture. Amphetamine use is associated with development of hypertension and heart failure related to reduced ejection fracture. Route of administration can cause specific problems. For instance, inhaled crack cocaine may lead to chemical pneumonitis, or "crack lung" [13]. Intranasal use of powder cocaine may lead to cartilaginous abnormalities related to vasoconstriction. A common adverse effect of smoking methamphetamine is dental decay related to combination of caries, bruxism, vasoconstriction of capillaries, and enamel exposure to chemicals. Finally, low birth weight is the most common fetal abnormality.

Opioids

Deaths related to opioid overdose have led to increased national focus on adverse effects of chronic opioid use. Routes of administration can lead to specific consequences. For instance, intravenous route has led to increased rates of communicable disease such as HIV and Hepatitis C, cardiovascular consequences such as endocarditis (due to bacteria injection and subsequent travel to heart valves), and local effects such as thrombophlebitis and cellulitis [14]. Subdermal use, commonly known as "skin-popping," can lead to localized cellulitis and abscess formation, as can intravenous use. Generally, opioid use is associated with multiple organ system involvement. Respiratory depression and sleep-disordered breathing are common, and respiratory depression is the cause of death in overdose. A frequent complaint of patients prescribed long-term opioids is constipation, and bowel hypomotility can also lead to small bowel obstruction [15]. Endocrine complications include hypogonadism (varies based on the opioid) and osteoporosis, though there is limited data about this [16]. Likely related to the up-regulation of mu-opioid receptors, opioid-induced hyperalgesia is a potential consequence of long-term opioid use, and possibly fibromyalgia [17]. Maternal-fetal complications include fetal withdrawal called Neonatal Abstinence Syndrome or NAS, low birth weight, and

preterm birth. Methadone, a specific treatment for opioid use disorder and for pain, and some other opioids carry a risk of prolonged QTc on EKG that can lead to vulnerability to develop the deadly arrhythmia Torsades de Pointes [18].

Cannabis

Potential health benefits and risks of cannabis have generated significant public interest. Common to other inhaled substances, cannabis smoke is a lung irritant and can affect patients with previous diagnoses such as asthma and COPD. Cannabis use has been associated with an increased risk of cerebrovascular accidents [19]. While commonly touted as a treatment for nausea, cannabis use, even in experienced users is linked to hyperemesis. Cessation of cannabis use will usually lead to improvement.

Tobacco

Tobacco use is most commonly linked to pulmonary disorders but also affect multiple other organ systems. Chronic nicotine use is associated with asthma, development of chronic obstructive pulmonary disease, and lung cancer. Smoking worsens coronary artery disease and hypertension, and increases stroke risk [20]. Ocular complications are possible. Specifically, smoking is associated with macular degeneration, cataracts, and blindness [21]. Maternal-fetal complications have been well-studied as tobacco use has demonstrated increased risk of ectopic pregnancy and low birth weight. The United States Preventive Services Task Force (USPSTF) recommends that male smokers with a greater than 30 pack/year smoking history between the ages of 65 and 75 years undergo abdominal ultrasound to evaluate for enlarged abdominal aorta [22]. Men and women between the ages of 55 and 80 years who have greater than 30 pack/year smoking history and have smoked within the last 15 years should receive an annual screening non-contrast Chest CT to evaluate for lung cancer [23].

PCP, Hallucinogens, Inhalants

This grouping of psychoactive substances is associated with primarily cognitive impairment with chronic use [24]. Evidence supporting fetal abnormalities is inconclusive [25].

Caffeine

Commonly used by working populations, there has been concern that caffeine can precipitate arrhythmias or increase cancer risk. Evidence on both accounts is conflicting [26]. However, insomnia is a common complication.

Review Questions

1. Karl is a 50-year-old male with history of alcohol use disorder. He is reviewing his recent laboratory results with his primary care physician, and the physician discusses labs that may indicate some effects on his body from his alcohol use. The most likely lab values they are discussing are:
   A. Increased platelet count
   B. Hyperalbuminemia
   C. Leukopenia
   D. Gamma glutamyltransferase (GGT)
   E. Decreased mean corpuscular volume

   Correct answer: D

   Explanation: Markers of synthetic liver function include albumin level, platelet count, and bilirubin. Patients with severe alcohol use disorder often have thrombocytopenia, hypoalbuminemia, and increased total bilirubin. Decreased white count is not a common finding in alcohol use disorder. Liver enzymes that can be elevated with alcohol use include Alanine transaminase (ALT) Aspartate transaminase (AST), as well as GGT. Elevations in GGT may be more specific to alcohol use. Mean corpuscular volume is often increased with chronic alcohol use due to megaloblastic anemia.
2. Candi is a 65-year-old female with a 40 pack/year smoking history. She is a current smoker. What does the United States Preventive Services Task Force (USPSTF) recommend regarding her tobacco use?
   A. Annual respiratory cultures
   B. Annual screening non-contrast CT Chest
   C. Biannual abdominal aorta ultrasound
   D. Measurement of liver transaminases
   E. None of the above

   Correct answer: B

   Explanation: USPFTF recommends annual screening non-contrast Chest CT for men and women above the age of 60 with >30 pack/year smoking history. Annual respiratory cultures are not indicated. USPFTF recommends men above the age of 65 who currently smoke with greater than 30 pack/year history to undergo abdominal aorta ultrasound. This recommendation does not apply to women.
3. Hector is a 78-year-old male with generalized anxiety disorder. He has been prescribed clonazepam 1 mg TID for the past 10 years by his primary care physician, but was referred to you, a psychiatrist, after his prescriber retired. During your discussion of the risks of benzodiazepine use, you mention which of the following?
   A. Thrombocytopenia
   B. Cognitive impairment, including dementia
   C. Elevated risk of skin cancer
   D. Cushing's syndrome
   E. Intractable vomiting

Correct answer: B

Explanation: Long-term use of benzodiazepines has significant health consequences. Notably, the increased fall risk has led to hip fractures in geriatric populations. Benzodiazepine use has also led to a near doubling of dementia risk. There is no association with skin cancer. There is no association with thrombocytopenia, Cushing's syndrome, or vomiting. Despite these consequences, prescribers should avoid rapid discontinuation, as this can lead to seizures, withdrawal-associated psychosis.

4. Barry is a 67-year-old guitar player in a band who began using heroin in the 1960s by inhalation, and quickly progressed to IV use for about 15 years. In the 1980s, he began treatment with methadone, and he remained abstinent from heroin for over two decades. Intravenous infectious complications of heroin use include which of the following?
   A. HIV
   B. Hepatitis A
   C. Increased fall risk
   D. Constipation
   E. Somnolence

   Correct answer: A

   Explanation: Intravenous heroin use is associated with blood-borne transmission of infections such as HIV and Hepatitis C. Sharing needles can also result in bacteremia, which requires parenteral antibiotics. While constipation is an effect of opioid use, it is not an infectious complication. Somnolence and concomitant increased fall risk is seen with opioid intoxication.
5. After ingesting an unidentified substance, Elmer quickly develops a stabbing feeling radiating to his back. Which emergency condition is most important to consider in your differential diagnosis, and what was the most likely substance involved?
   A. GERD; alcohol
   B. Pneumonia; cannabis
   C. Aortic dissection; cocaine
   D. Appendicitis; nicotine
   E. Deep venous thrombosis; cannabis

   Correct answer: C

   Explanation: Cocaine intoxication can cause coronary vasospasm, myocardial infarction, and aortic dissection. Prompt diagnosis and treatment is crucial. None of the other answers are relevant. GERD and pneumonia are not conditions that require emergent treatment. Appendicitis is not a complication of nicotine use.

References

1. Koguchi K, Nakatsuji Y, Abe K, Sakoda S. Wernicke's encephalopathy after glucose infusion. Neurology. 2004;62(3):512.

2. Malamud N, Skillicorn SA. Relationship between the Wernicke and the Korsakoff syndrome; a clinicopathologic study of seventy cases. AMA Arch Neurol Psychiatry. 1956;76(6):585–96.
3. Beilin LJ, Puddey IB. Alcohol and hypertension: an update. Hypertension. 2006;47(6):1035–8.
4. Wood AM, Kaptoge S, Butterworth AS, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. Lancet. 2018;391(10129):1513–23.
5. Runyon BA. A primer on detecting cirrhosis and caring for these patients without causing harm. Int J Hepatol. 2011;2011:801983.
6. Latvala J, Parkkila S, Niemelä O. Excess alcohol consumption is common in patients with cytopenia: studies in blood and bone marrow cells. Alcohol Clin Exp Res. 2004;28(4):619–24.
7. Joya X, Friguls B, Ortigosa S, et al. Determination of maternal-fetal biomarkers of prenatal exposure to ethanol: a review. J Pharm Biomed Anal. 2012;69:209–22.
8. Girard DE, Kumar KL, McAfee JH. Hematologic effects of acute and chronic alcohol abuse. Hematol Oncol Clin North Am. 1987;1(2):321–34.
9. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med. 2009;169(21):1952–60.
10. Chan TT, Leung WC, Li V, et al. Association between high cumulative dose of benzodiazepine in Chinese patients and risk of dementia: a preliminary retrospective case-control study. Psychogeriatrics. 2017;17(5):310–6.
11. Wikner BN, Källén B. Are hypnotic benzodiazepine receptor agonists teratogenic in humans? J Clin Psychopharmacol. 2011;31(3):356–9.
12. Bhattacharya P, Taraman S, Shankar L, Chaturvedi S, Madhavan R. Clinical profiles, complications, and disability in cocaine-related ischemic stroke. J Stroke Cerebrovasc Dis. 2011;20(5):443–9.
13. Devlin RJ, Henry JA. Clinical review: major consequences of illicit drug consumption. Crit Care. 2008;12(1):202.
14. Schranz AJ, Fleischauer A, Chu VH, Wu LT, Rosen DL. Trends in drug use-associated infective endocarditis and heart valve surgery, 2007 to 2017: a study of statewide discharge data. Ann Intern Med. 2018;170:31.
15. Thörn SE, Wattwil M, Lindberg G, Säwe J. Systemic and central effects of morphine on gastroduodenal motility. Acta Anaesthesiol Scand. 1996;40(2):177–86.
16. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2018;103(5):1715–44.
17. Keefer L, Drossman DA, Guthrie E, et al. Centrally mediated disorders of gastrointestinal pain. Gastroenterology. 2016.
18. Pearson EC, Woosley RL. QT prolongation and torsades de pointes among methadone users: reports to the FDA spontaneous reporting system. Pharmacoepidemiol Drug Saf. 2005;14(11):747–53.
19. Hackam DG. Cannabis and stroke: systematic appraisal of case reports. Stroke. 2015;46(3):852–6.
20. Neunteufl T, Heher S, Kostner K, et al. Contribution of nicotine to acute endothelial dysfunction in long-term smokers. J Am Coll Cardiol. 2002;39(2):251–6.
21. Solberg Y, Rosner M, Belkin M. The association between cigarette smoking and ocular diseases. Surv Ophthalmol. 1998;42(6):535–47.
22. Ali MU, Fitzpatrick-Lewis D, Miller J, et al. Screening for abdominal aortic aneurysm in asymptomatic adults. J Vasc Surg. 2016;64(6):1855–68.
23. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395–409.
24. Hinsberger A, Sharma V, Mazmanian D. Cognitive deterioration from long-term abuse of dextromethorphan: a case report. J Psychiatry Neurosci. 1994;19(5):375–7.
25. Mvula MM, Miller JM, Ragan FA. Relationship of phencyclidine and pregnancy outcome. J Reprod Med. 1999;44(12):1021–4.
26. Tang N, Wu Y, Zhou B, Wang B, Yu R. Green tea, black tea consumption and risk of lung cancer: a meta-analysis. Lung Cancer. 2009;65(3):274–83.

Co-occurring Psychiatric Disorders

22

Caridad Ponce Martinez

High-Yield Review Points

- The presence of co-occurring psychiatric disorders and substance use disorders is associated with worse outcomes for both disorders.
- Adequate treatment has been shown to improve outcomes for both disorders, in varying degrees.
- Given the diagnostic challenges in patients with co-occurring disorders, assessment should occur via serial, longitudinal assessments, and using multiple information sources.
- Treatment of co-occurring disorders should be integrated.
- Treatment of both disorders should be based on a long-term perspective, and should consider pharmacologic and psychosocial interventions.

Introduction

The presence of both psychiatric and substance use disorders in a patient is referred to as co-occurring disorders (COD), and is associated with worse outcomes in both the psychiatric disorder and the substance use disorder. The negative outcomes include higher rates in both disorders for relapse, hospitalization, violence, incarceration, homelessness, infections, underachievement and failure in work and school, and treatment noncompliance [1–4]. One contributing factor is that the treatment for substance use disorders (SUDs) and psychiatric disorders is often offered in parallel or consecutive systems, rather than integrated systems where both

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disorders can be addressed simultaneously. This can make it challenging for patients to access the services they need and the fragmentation in services can increase the likelihood of treatment non-adherence [2, 4]. Some of the psychiatric symptoms present in patients seeking treatment may be the result of the substance itself, and resolve completely within days or weeks following abstinence [5].

Epidemiology

Two major epidemiologic studies have provided information about the prevalence of substance use disorders and psychiatric disorders in the United States, the Epidemiologic Catchment Area (ECA) study and the National Comorbidity Survey (NCS). Other important studies include the National Longitudinal Alcohol Epidemiologic Survey (NLAES) and the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) [5]. A systematic review and meta-analyses found strong associations between co-occurring SUDs with major depression and any anxiety disorder. The strongest associations were found between illicit drug use and major depression, followed by illicit drug use and any anxiety disorder and alcohol use and any anxiety disorder [6].

In reviewing prevalence data, patients' setting has a considerable impact, as the prevalence of co-occurring disorders is lowest in people living in the community (3–4%), higher in individuals seeking mental health treatment (40–60%), and highest in people in substance use treatment settings (50–60%). Patients with severe and persistent mental illness have particularly high rates of co-occurring SUDs. For example, up to 75–90% of patients with schizophrenia are likely to use nicotine, and the prevalence of tobacco use is only slightly lower in patients with bipolar disorder (55–70%). Of note, nicotine is not routinely included in epidemiological assessments of SUDs [4].

Major depression is the most common COD among patients presenting for treatment of SUDs. Although bipolar disorder is less common in this group, the presence of bipolar disorder increases the likelihood of an SUD fourfold. The high rates of association could be an artifact of treatment seeking and result in an overestimate of prevalence data (selection bias), so it is important to also compare them with community samples drawn from the general population [5].

(a) *Epidemiologic Catchment Area Study*

The National Institutes of Mental Health's ECA study (1980–1984) determined the prevalence of comorbid alcohol, other drug and mental disorders among 20,291 persons in community and institutional settings using Diagnostic and Statistical Manual IV (DSM-IV) criteria for diagnoses. Lifetime prevalence rates in persons interviewed by the ECA program were 22.5% for any non-substance use mental disorder, 13.5% for alcohol abuse or dependence, and 6.1% for other drug abuse or dependence. Among those with a lifetime mental disorder, there was an association of more than twice the risk of having an alcohol use disorder and over four times the

risk of having another drug use disorder. Abuse or dependence of one addictive substance increases the risk of abuse or dependence on another addictive substance by seven times. Patients with drug disorders (abuse or dependence) were more likely (53%) to have a comorbid mental disorder compared to patients with alcohol disorders (37%) [7].

One interesting finding of the ECA is that individuals treated in clinical settings (specialty mental health or addiction settings) have significantly higher odds of having comorbid disorders, perhaps related to the severity of their symptoms or the impairment in function. Among the institutional settings, comorbidity of addictive and severe mental disorders was highest in the prison population, most notably related to diagnoses of antisocial personality disorder, schizophrenia, and bipolar disorder [7].

In terms of specific diagnoses, schizophrenia was associated with nearly five times higher risk of having an SUD, when compared to the general population. Antisocial personality disorder increased the likelihood of substance abuse and substance dependence. The anxiety disorders more likely to have comorbid SUDs include phobias, panic disorder, and OCD. Bipolar disorder is more likely to have comorbid SUD when compared with major depression [4, 7].

(b) *National Comorbidity Survey Replication*

The NCS-R was a national survey of households conducted between February 2001 and April 2003 using a fully structured diagnostic interview to assess 12-month prevalence, severity and comorbidity of anxiety, mood, impulse-control, and substance disorders among adults in noninstitutionalized settings. The DSM-IV was used as diagnostic criteria, and schizophrenia was excluded. About one-quarter of the total sample met criteria for any disorder, and among these, 55% of participants had a single diagnosis. The authors concluded that although mental disorders are widespread, the serious cases are concentrated among a relatively small proportion of highly comorbid cases. The odds ratio of a comorbid lifetime mental illness and any lifetime SUD was 2.4 [4, 8].

Assessment and Diagnosis

One of the most challenging questions facing clinicians working with patients with co-occurring disorders is when to make a diagnosis of either disorder. Depending on the treatment setting, a patient may present intoxicated, experiencing withdrawal symptoms, or in varying lengths of abstinence. In these situations, psychiatric symptoms present could be the result (or exacerbated) by the presence or absence of the substance. Some of the psychiatric symptoms present in patients seeking treatment may be the result of the substance itself, and resolve completely within days or weeks following abstinence [5]. For example, symptoms of anxiety present while a patient is experiencing alcohol withdrawal could well be attributed to the withdrawal syndrome, and expected to resolve completely once the patient is no longer

in withdrawal. However, if anxiety is part of a primary psychiatric disorder, symptoms are likely to persist beyond the alcohol intoxication and withdrawal, and may interfere with the alcohol use disorder (AUD) treatment. Additionally, the varying levels of severity of each disorder contributes to the heterogeneity in clinical presentations [9]. Assuming an etiological diagnosis (i.e., treating one disorder will resolve the other disorder) when assessing patients with CODs may result in insufficient treatment of both disorders.

Assessment of patients with CODs should ideally occur via serial, longitudinal assessments, and utilizing multiple sources to gather data (i.e., semi-structured interviews, collateral information, laboratory testing, and physical examination). In patients with chronic substance use, serious and persistent mental illness and medical comorbidities, cognitive impairment may add to diagnostic challenges. The goal is to avoid under-diagnosis, for example, by believing that treatment of the AUD will automatically relieve the anxiety disorder (i.e., etiological diagnosis) as well as over-diagnosis, for example, diagnosing a primary psychotic disorder and a stimulant use disorder in a patient who only experiences psychosis when intoxicated.

One important way to avoid over-diagnosis is to understand the time course during which particular substances can induce psychiatric symptoms. Diagnosis should occur at minimum once the individual is no longer in active withdrawal. For most substances, this is typically 2–4 weeks after acute withdrawal, but with methamphetamine and alcohol-induced psychoses, it may be necessary to wait several months. Given the epidemiological data, it is more likely that patients will have COD than etiological diagnoses [4]. For psychotic symptoms in particular, a common diagnostic criterion used in research and clinical practice is that psychotic symptoms must persist for at least 1 month following cessation of substance use, in order to make a diagnosis of a primary co-occurring psychotic disorder [5].

Clinicians should also consider the severity of the presenting symptoms into their assessment. Regardless of whether presenting psychiatric symptoms are the result of a co-occurring psychiatric disorder or substance-induced, their severity may require immediate action. For example, although substance-induced depression can resolve rapidly, it can be as dangerous as major depressive disorder in terms of the higher risk of suicide and self-injurious behavior [5]. Similarly, symptoms of anxiety and psychosis related to substances may be so impairing as to require immediate attention, regardless of their etiology.

A complete assessment provides screening for co-occurring psychiatric and substance use disorders, medical comorbidities, and risky behaviors (suicide attempts, violence, sexual practices, intravenous needle use). Additionally, it seeks to fully comprehend the extent of the disorders, by not only evaluating the acute risks, but also the scope of the patient's disability and their personal/environmental resources to help guide their recovery. Finally, understanding of a patient's motivation for change and stage of recovery helps clinicians guide their interventions to better match the patient's readiness for treatment [9].

Treatment

There is limited high-quality evidence to evaluate treatment of individuals with co-occurring psychiatric and substance use disorders. However, the cumulative evidence from more than 25 studies completed over the past three decades strongly supports the integration of psychiatric and substance use treatments as more effective, compared to services offered in a separate or parallel fashion [2, 3]. This means that the most effective interventions are combined at the clinical interface, with the same clinicians or clinical team providing appropriate mental health and substance use interventions in a way that is coordinated and guides patients in learning to manage both illnesses. The strategies of treatment are to engage people in treatment of both disorders, to use pharmacologic and psychosocial interventions that are matched to a patient's stage of change, and to consider a long-term perspective in treatment [3]. Components may include social skills training, family psychoeducation interventions, and peer-oriented groups [2].

In traditional parallel or sequential treatment, the burden of establishing and following a treatment plan often falls on the patient, with lack of improvement of one illness frequently impeding the ability to access treatment for the other illness [10]. Different funding sources for agencies treating either disorder can affect the ability to provide integrated services. However, the Mental Health Parity and Addiction Equality Act and the Affordable Care Act have mandated increased availability for behavioral health and SUD treatment services, [11] which could result in improved integration of services.

Specific pharmacologic information for each psychiatric disorder is presented below. A Cochrane review including 32 randomized controlled trials found no compelling evidence to support any one psychosocial intervention over another for people to remain in treatment, reduce substance use, or improve their mental state, when serious psychiatric illness is involved. It should be noted that methodological difficulties existed that hindered pooling of the results, so these results should be interpreted with caution [12].

General principles of treatment of CODs are to consider the patient's stage of motivational engagement (i.e., will treatment be focused on abstinence or harm-reduction?); treat both disorders simultaneously and aggressively for the best outcomes in both disorders; select treatments including medications that could potentially treat both disorders; prioritize use of medications that have the least liability for abuse/addiction; monitor for potential toxicity or interactions with other medications or substances of abuse; and monitor closely for treatment adherence [4].

(a) *Mood disorders*

Initiation of treatment for the SUD should always be an important part of the treatment for a patient with co-occurring mood and SUDs. However, for patients with a primary mood disorder, abstinence alone will not be sufficient to improve the mood symptoms [5].

In the treatment of co-occurring depression, antidepressants are not uniformly effective in improving mood. There is some evidence showing their superiority over placebo in patients with co-occurring AUD, but the evidence is less consistent in patients with OUD or cocaine use disorder. Antidepressants appear to improve SUD outcomes only when depression outcomes improve. Meta-analyses suggest there is more consistent efficacy in the treatment of depression in this population with mixed-mechanism antidepressants than for selective serotonin reuptake inhibitors (SSRIs), although tricyclic antidepressants have a potential for toxicity. SSRIs should be used cautiously or avoided in patients with depression and co-occurring early-onset AUDs, given their association with worse drinking outcomes in the early-onset type of alcohol dependence [4]. This should be balanced with the fact that SSRIs are generally well tolerated and have a relatively benign side-effect profile [5]. Medications for treatment of the SUDs should also be considered. By improving substance use, these medications may also reduce substance-induced depressive symptoms, and thus improve mood, reduce stress, and improve overall functioning [5].

Psychosocial treatments studied include motivational interviewing, which can improve treatment engagement and retention, cognitive behavioral therapy (CBT), a community reinforcement approach (CRA), voucher incentives, and 12-step facilitation. Both CBT and CRA appear effective at both decreasing depressive symptoms and substance abuse [4].

Indirect evidence has suggested that anticonvulsants such as valproic acid and carbamazepine should be selected over lithium as first-line agents in the treatment of patients with bipolar disorder and co-occurring SUDs. This stems from studies finding that substance abuse predicts a poor response to lithium and that the variants of bipolar disorder (mixed or rapid-cycling) are more prevalent among patients with co-occurring disorders and also more likely to respond to anticonvulsants. There is also some evidence that valproic acid can have positive effects on AUD independent of its effects on mood improvement [13].

In patients with suicidal ideation, however, lithium remains the only mood stabilizer with an anti-suicidal effect, and thus may be preferred over anticonvulsants. There is less robust evidence for effectiveness in this population of lamotrigine, gabapentin, and second-generation antipsychotics. Of note, both quetiapine and aripiprazole have shown improvements in mood and substance use outcomes [5]. Use of psychosocial treatments can further enhance treatment, particularly with CBT. Two CBT approaches have been used specifically for patients with co-occurring SUDs and bipolar disorder, Integrated Group Therapy (IGT) and CBT plus medication monitoring.

(b) *Anxiety disorders*

Generalized anxiety disorder (GAD), panic disorder, and social anxiety disorder are the most common anxiety disorders that can co-occur with SUDs and they are the most studied. SSRIs are generally considered first-line medications due to their tolerability, safety, and effectiveness in the treatment of anxiety disorders; SNRIs

are considered alternate first-line. Other medications that can be used include mirtazapine (some promise in treatment of panic disorder and social anxiety disorder), buspirone (most helpful in treatment of uncomplicated generalized anxiety disorder), pregabalin (some evidence in treatment of GAD), gabapentin (some promise in treatment of social anxiety disorder), beta blockers (no controlled trials support efficacy in treatment of GAD), and clonidine (reduces acute opioid withdrawal symptoms including anxiety) [5].

There is very limited evidence for the use of atypical antipsychotics in the treatment of anxiety disorders, despite their widespread use; associated weight gain and the risk of metabolic syndrome are significant considerations. Benzodiazepines should generally be avoided in this population, particularly when there is active substance use, given the risk of misuse and short-term efficacy. In patients with a history of SUD, benzodiazepines should be used with caution, closely monitored, and longer-acting agents with lower abuse potential such as oxazepam and chlordiazepoxide may be considered. Finally, patients with panic disorder and comorbid stimulant use disorder (such as cocaine), may respond well to anticonvulsants, due to a hypothesized neuronal sensitization mechanism induced by repeated stimulant administration [5].

Psychosocial treatments studied for co-occurring SUDs and anxiety disorders include CBT, mindfulness, acceptance-based treatments, and 12-step groups. Of these CBT is among the most effective interventions, resulting in improvement of both anxiety disorders and SUDs [4, 5].

(c) *Psychotic disorders*

There is insufficient evidence to guide treatment of psychotic disorders in patients with comorbid substance use disorders. Some studies suggest that atypical or second-generation antipsychotics are preferable to typical or first-generation antipsychotics, due to treatment of negative symptoms as well as reduction of substance use and craving, but there have been other studies showing no difference between atypical and typical antipsychotics [4, 5]. Among the atypical antipsychotics, clozapine is one of the most studied medications for treatment of co-occurring schizophrenia and SUDs. Although the evidence is limited to case reports and correlational studies, clozapine decreased use of alcohol, nicotine, cannabis, cocaine and other drugs of abuse, in addition to its well-established efficacy in treating psychosis. There are, however, no randomized controlled clinical trials demonstrating its superiority over other antipsychotics [4]. Other antipsychotics studied include risperidone [14], olanzapine, quetiapine, and aripiprazole [4]. Interestingly, some patients with co-occurring schizophrenia and SUDs are more likely to experience EPS with antipsychotic medications, which may indicate closer clinical monitoring for side effects as a way to enhance medication compliance.

Psychosocial treatments specific for co-occurring schizophrenia and SUD have been identified. They include dual recovery therapy, modified cognitive behavioral therapy, modified motivational enhancement therapy, the Substance Abuse Management Module, and Behavioral Treatment for Substance Abuse in Severe and

Persistent Mental Illness (BTSAS). These treatments include components of motivational interviewing, relapse prevention, and social skills training; they also encourage participation in 12-step programs such as Alcoholics Anonymous. BTSAS, for example, delivers treatment in an outpatient small group setting, involving elements of motivational interviewing, contingency management, and structured goal setting, with the purpose not only of decreasing substance use but also providing social skills training, psychoeducation, and relapse prevention for both disorders [4].

(d) *Trauma-related disorders*

Dysregulation of the hypothalamic-pituitary axis and the noradrenergic systems has been identified as a common pathway for PTSD and SUDs. Although most of the available evidence for these CODs focuses on treatment for the symptoms of PTSD, there is some evidence that individuals can benefit from interventions that primarily target the SUDs. Patients with CODs respond to standard pharmacotherapies in treatment of PTSD comparably to patients with only PTSD. Sertraline and paroxetine are FDA-approved for treatment of PTSD. One important consideration is that patients with "type B" alcoholism (severe alcohol problems, high levels of comorbid psychopathology, early-onset alcoholism), SSRIs may produce worse outcomes compared to placebo [5].

Among psychotherapies, three different types of cognitive behavioral therapy (exposure-based therapy, cognitive-focused therapy, and anxiety/stress management therapy) have been studied. Seeking Safety is one of the most widely known and studied type of integrated CBT. It is a manualized treatment consisting of 25 sessions, initially developed as a group modality for adult women, but has since expanded to other populations and to individual therapy [5].

(e) *Attention-deficit and hyperactivity disorder*

Much has been written regarding the importance of effective treatment of ADHD as a way to prevent teenage and young adult use of substances. This stems from evidence that children with untreated ADHD are more likely to use substances recreationally. Similarly, untreated ADHD may negatively affect the course of SUD and interfere with treatment [5].

Given the abuse potential of medications used to treat ADHD, especially stimulants, parents and medical providers are often concerned that treatment of ADHD with stimulants may lead to substance abuse in adults. Although there is no increased risk of this occurring, the risks of a stimulant prescription must be considered, especially for patients with SUDs. One strategy is to prescribe long-acting preparations of stimulants that may have lower abuse potential and may be of particular utility for patients with co-occurring ADHD and SUDs. The lower abuse potential stems from a slower rate of onset of the drug's effects, less positive subjective drug effects, and increased difficulty using via a non-oral route [5].

In patients with co-occurring ADHD and SUDs, one proposed strategy has been to classify patients into groups of low, moderate, and severe risk for misuse or diversion [5]. In the high-risk group, non-stimulant medications can be the first choice in

treatment of ADHD; long-acting formulations of stimulants (methylphenidate skin patch or crush-resistant pill form, lisdexamphetamine) can be considered when non-stimulants are not effective.

Stimulants have also been considered for treatment of some SUDs, particularly cocaine and amphetamines, with mixed results. Dextroamphetamine has had the most consistent positive effects in treatment of cocaine use disorder, as well as in substitution treatment of amphetamine dependence [5]. Despite this evidence, use of stimulants in this population is a controversial topic, and should be done with close clinical monitoring to decrease the risk for diversion or misuse.

(f) *Personality disorders*

The presence of a personality disorder in patients with CODs can complicate and negatively affect the course of treatment of the SUD, and is associated with non-adherence and increased risk of relapse. It is not the specific personality disorders but their severity that is the best predictor of therapeutic outcomes [5].

In terms of treatment, the goal is to minimize the impact of the personality disorder. This is best accomplished in a structured and integrated system, employing both pharmacotherapy (when indicated) and psychosocial/psychotherapeutic interventions. Patients with personality disorders are at increased risk of polypharmacy in their treatment, so symptom-targeted psychotherapy should occur as an adjunct to psychosocial interventions. Treatment focuses on increasing the therapeutic alliance, performing risk assessments, and addressing the motivational and interpersonal problems that contribute to both co-occurring disorders. No specific medications have been studied for treatment of comorbid SUDs and personality disorders. Some psychotherapies have been developed, including a modified version of Dialectical Behavior Therapy (DBT), DBT-S, which includes the standard DBT components, focuses on abstinence and the therapeutic alliance, and seeks to improve motivation for change [5].

(g) *Eating disorders*

Eating disorders may be overlooked when assessing for co-occurring disorders with SUDs. Depending on the severity of the eating disorder, medical stabilization may be necessary prior to initiation of treatment for the SUD. Therefore, screening should occur in all patients undergoing treatment for an SUD [5]. No specific pharmacotherapy or psychotherapy interventions have been studied when both disorders are present.

Outcomes

Functional imaging studies in patients with SUDs reveal dopaminergic reductions in the basal prefrontal regulation of behavior. It is unclear if these are the result of chronic substance use or if underlying deficits in psychiatric conditions (ADHD, schizophrenia) make substances more salient and rewarding, increasing the

likelihood of abuse [5]. Given the likely common pathways contributing to COD, it makes sense to treat both as a way to improve outcomes for both disorders.

Treatment of SUDs and comorbid mood disorders, psychotic disorders, anxiety disorders, eating disorders, PTSD and other trauma-related disorders has been shown to improve outcomes for both disorders (i.e., reductions in psychiatric symptoms and in substance use), although in varying degrees. The inverse, lack of treatment, has definitely been shown to worsen outcomes. Untreated major depression among patients with SUDs, for example, has been associated with worse substance use outcomes, worse psychiatric symptoms, and increased risk of suicide [5]. In some patients, use of antidepressants not only appears to reduce symptoms of depression, but also of AUD. In psychotic disorders, although both typical and atypical antipsychotics can improve psychotic symptoms, only atypical antipsychotics have shown some benefit in reducing craving or substance use. Clozapine in particular appears to be the most effective antipsychotic medication in terms of substance abuse [15]. The combination of AUD and anorexia nervosa is a strong predictor of a fatal outcome, and recovery rates for both disorders are generally poor. On the other hand, patients with comorbid bulimia nervosa and SUD have similar treatment outcomes to patients without a history of SUD, although the presence of binge eating tends to confer worse outcomes.

Review Questions

1. Ms. Lopez is a 43-year-old female who has enrolled in an intensive outpatient program, and reports drinking about 1 bottle of wine per day for the past 15 years, occasionally "losing count" of how much she drinks on the weekends, having fights with her children about her alcohol use, and having multiple crying spells per week that often end in thoughts of "it would be easier if I just didn't wake up." Which of the following diagnoses is the most common psychiatric comorbidity among patients presenting for treatment of substance use disorders?
   A. Bipolar disorder
   B. Borderline personality disorder
   C. Generalized anxiety disorder
   D. Major depressive disorder
   E. Schizophrenia

   Answer: D.

   Explanation: Major depressive disorder is the most common psychiatric diagnosis among patients presenting for treatment of an SUD. Bipolar disorder is less common in this group, but its presence increases the likelihood of a SUD by at least four times. Among patients in institutional settings, the highest psychiatric comorbidity was found to be in the prison population, most notably related to diagnoses of antisocial personality disorder, bipolar disorder, and schizophrenia.

(See The ASAM principles of addiction medicine; Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study.)

2. Mr. Smith is a 35-year-old male recently released from jail after his second charge of driving under the influence of alcohol and cocaine. For many years he has struggled with periods of irritability and high energy, during which he doesn't need to sleep and makes very impulsive decisions, often followed by periods of severe depression. He drinks up to 1 pint of vodka per day during most days of the week and has recently been using cocaine more frequently. Which of the following is true about epidemiological studies examining the prevalence of substance use disorders and psychiatric disorders in the United States?
   A. The Epidemiologic Catchment Area (ECA) study examined prevalence data among adults in both community and institutionalized settings.
   B. The National Comorbidity Survey Replication (NCS-R) was a follow-up study to collect information about changes in psychiatric and substance use disorders.
   C. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) has been conducted in six consecutive waves to evaluate substance use across the lifetime.
   D. The National Longitudinal Alcohol Epidemiologic Survey (NLAES) sampled the alcohol use of adults in institutionalized and household settings.
   E. The National Longitudinal Illicit Drug Epidemiologic Survey (NLIDES) sampled household participants 16 years of age and older, to account for teenage cannabis use.

   Answer: A.

   Explanation: The ECA is the only one of these epidemiological surveys to sample adults in both community and institutional settings. The NCS-R was a study done with more than 9000 new participants rather than re-interviews. The NESARC is a third-generation epidemiologic survey, with wave 1 conducted in 2001–2002 and wave 2 conducted 2004–2005, including more than 30, 000 of the original participants. The NLAES was a household survey and did not include adults in institutionalized settings. Option e is not an actual epidemiologic study.

   (See The ASAM principles of addiction medicine; The American Psychiatric Publishing textbook of substance abuse treatment; Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study; Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication.)

3. Thomas is a 52-year-old male recently admitted to the psychiatric unit following a suicide attempt. He had previously required medical stabilization including admission to the intensive care unit due to delirium tremens from alcohol and for cardiac monitoring related to his intentional drug overdose. Initial evaluation reveals symptoms of depression, continuous alcohol use since age 12, and a strong family history of alcohol use disorder (AUD). Which of the following is the next best step in his treatment?

A. Offer no medications or treatment for depression, and refer the patient to an inpatient substance use treatment facility, as his depression is unlikely to improve if he continues to drink alcohol.
B. Initiate any antidepressant, as his AUD will likely subside if he has been "self-medicating" his depression.
C. Initiate amitriptyline, which can be helpful in treating depression and insomnia, and is inexpensive.
D. Initiate an antidepressant in the SSRI category, as they have been shown to improve depression and alcohol use in early-onset, severe AUD.
E. Initiate a mixed-mechanism antidepressant, which meta-analyses suggest are more efficacious in treating depression in this population.

Answer: E.

Explanation: For patients with a primary mood disorder, abstinence alone is unlikely to resolve symptoms of depression. Option b is incorrect because antidepressants appear to improve AUD outcomes only if depression also improves. Amitriptyline would not be a first-line agent in this patient, and likely should be avoided, given the potential risk for toxicity. SSRIs should be used with caution or avoided in patients with depression and early-onset alcohol use disorder, stronger family history of AUD, and more severe dependence, as drinking could worsen. Meta-analyses suggest there is more consistent efficacy in the treatment of depression with mixed-mechanism antidepressants than for SSRIs.

(See The ASAM principles of addiction medicine; The American Psychiatric Publishing textbook of substance abuse treatment.)

4. Ms. Evans is a 29-year-old female who is presenting for evaluation and treatment of opioid use disorder. She was recently treated for infectious endocarditis stemming from intravenous heroin use. She describes struggling with recurrent nightmares of previous sexual trauma, flashbacks near daily of her assault, being easily startled, and avoidance of any sexual activity with her partner. Use of opioids has previously provided some respite from these symptoms, but she wishes to stop using illicit drugs. Which of the following psychotherapies was developed specifically for treatment of co-occurring posttraumatic stress disorder (PTSD) and substance use disorders?
A. Seeking Safety
B. Mindfulness-based stress reduction
C. Dual recovery therapy
D. Integrated group therapy
E. Acceptance and commitment therapy

Answer: A.

Explanation: Seeking Safety is one of the most widely known and studied type of integrated CBT, developed specifically for co-occurring PTSD and substance use disorders. Mindfulness-based stress reduction is a type of treatment focused on anxiety and stress management, but does not specifically address PTSD. Dual recovery therapy blends traditional addiction and psychiatric treat-

ment, based on the patient's stage of recovery, but does not specifically address symptoms of PTSD. Integrated group therapy is a type of CBT approach that has been used specifically for patients with co-occurring SUDs and bipolar disorder. Acceptance and commitment therapy involves mindfulness strategies but is also not specific for PTSD.

(See The ASAM principles of addiction medicine; The American Psychiatric Publishing textbook of substance abuse treatment.)

5. Mr. Fernandez is a 60-year-old male presenting to his primary care physician for treatment of low energy and motivation, increased crying spells, decreased appetite, increased isolation, and poor self-care. He was recently fired from his job because of unexcused absences. He has struggled with similar episodes since his twenties, but never sought treatment. For the past 40 years, he has been drinking an average of 6–18 beers daily after work, and admits to drinking until he "passes out" recently, as a way to help him fall asleep. Based on available epidemiological data, which of the following psychiatric disorders is most likely to have co-occurring SUD (excluding tobacco use disorder) among patients presenting for treatment?
   A. Mood disorders
   B. Anxiety disorders
   C. Trauma-related disorders (e.g., PTSD)
   D. Personality disorders
   E. Attention-deficit and hyperactivity disorder

   Answer: A.

   Explanation: Mood disorders (major depression, more specifically) is the most common co-occurring psychiatric disorder among patients presenting for treatment of SUDs. Although bipolar disorder is less common in this group, the presence of bipolar disorder increases the likelihood of an SUD by at least four times. In institutional settings, particularly the prison population, co-occurring severe psychiatric disorders and SUDs is most notably related to diagnoses of antisocial personality disorder, schizophrenia, and bipolar disorder.

   (See The ASAM principles of addiction medicine; Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA: the journal of the American Medical Association.)

References

1. Najt P, Fusar-Poli P, Brambilla P. Co-occurring mental and substance abuse disorders: a review on the potential predictors and clinical outcomes. Psychiatry Res. 2011;186(2–3):159–64.
2. Drake RE, Mueser KT, Brunette MF, McHugo GJ. A review of treatments for people with severe mental illnesses and co-occurring substance use disorders. Psychiatr Rehabil J. 2004;27(4):360–74.
3. Brunette MF, Mueser KT. Psychosocial interventions for the long-term management of patients with severe mental illness and co-occurring substance use disorder. J Clin Psychiatry. 2006;67(Suppl 7):10–7.

4. Galanter M, Kleber HD, Brady K. The American Psychiatric Publishing textbook of substance abuse treatment. 5th ed. Washington, DC: American Psychiatric Publishing; 2015. xix, 960 pages p.
5. Ries R, Miller SC, Saitz R, Fiellin DA, American Society of Addiction Medicine. The ASAM principles of addiction medicine. 5th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2014. xli, 1795 pages p.
6. Lai HM, Cleary M, Sitharthan T, Hunt GE. Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990-2014: a systematic review and meta-analysis. Drug Alcohol Depend. 2015;154:1–13.
7. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) study. JAMA. 1990;264(19):2511–8.
8. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):617–27.
9. Buckley PF. Prevalence and consequences of the dual diagnosis of substance abuse and severe mental illness. J Clin Psychiatry. 2006;67(Suppl 7):5–9.
10. Burnam MA, Watkins KE. Substance abuse with mental disorders: specialized public systems and integrated care. Health Aff (Millwood). 2006;25(3):648–58.
11. Priester MA, Browne T, Iachini A, Clone S, DeHart D, Seay KD. Treatment access barriers and disparities among individuals with co-occurring mental health and substance use disorders: an integrative literature review. J Subst Abus Treat. 2016;61:47–59.
12. Hunt GE, Siegfried N, Morley K, Sitharthan T, Cleary M. Psychosocial interventions for people with both severe mental illness and substance misuse. Cochrane Database Syst Rev. 2013;10:CD001088.
13. Salloum IM, Cornelius JR, Daley DC, Kirisci L, Himmelhoch JM, Thase ME. Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism: a double-blind placebo-controlled study. Arch Gen Psychiatry. 2005;62(1):37–45.
14. Temmingh HS, Williams T, Siegfried N, Stein DJ. Risperidone versus other antipsychotics for people with severe mental illness and co-occurring substance misuse. Cochrane Database Syst Rev. 2018;1:CD011057.
15. Drake RE, Mueser KT, Brunette MF. Management of persons with co-occurring severe mental illness and substance use disorder: program implications. World Psychiatry. 2007;6(3):131–6.

Prevention, Public Health, and Public Policy

23

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High-Yield Review Points

- Prevention of substance use disorders (SUDs) applies research-driven interventions and policies that target individual-level and community-level factors that can be modified to decrease risky substance use behavior that may lead to a substance use disorder.
- Public health allows us to identify, understand and reduce high-risk drug-using behaviors, promote SUD screening and treatment, and address underlying factors that may contribute to the societal burden of addiction, including poverty, stigma and discrimination, health inequities and inadequate access to medication treatment.
- Public policy involves regulations, rules, and laws designed to achieve a public benefit through shaping or controlling drug availability/access, use, and environmental factors that shape access and use.

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Introduction

The addiction psychiatrist is well positioned to advocate for and influence addiction-related public health efforts and policies to prevent substance use disorders and improve treatment outcomes at community and population levels. In this chapter, we describe approaches that clinicians can use to leverage their power to impact community health through prevention, public health, and policy. We frame prevention, public health, and public policy as interrelated approaches to reduce the societal impact and burden of substance use disorders.

Prevention

Prevention is a core health principle and clinical approach to avert or decrease the likelihood of a poor health outcome. Prevention traditionally has been conceptualized into three categories: primary, secondary, and tertiary. Primary prevention includes clinical and nonclinical interventions that reduce the likelihood that a substance use disorder will develop, whereas secondary prevention includes screening for SUD and efforts to improve health and reduce deterioration of health (e.g., treatment of comorbid conditions) and reducing complications from ongoing use among individuals who may not be ready for medication treatment for their addiction. Tertiary prevention includes efforts aimed at improving quality of life, reducing disease progression, and aiding symptom management. In this chapter, we will consider these avenues of prevention and clinical and nonclinical approaches to reducing the burden of substance use disorders at individual, community, and population levels.

Public Health

Public health refers to the discipline of promoting health and well-being within a population through efforts that target individual, community, societal, environmental, and policy levels. Public health is founded on research to understand and reduce factors that undermine health and promote factors that favor good health. Public health operates at local, regional, national, and global scales that require integrated approaches and transdisciplinary collaboration. Prevention is a key tenet of public health. Public health promotes the best health of a community or population through scaling up and disseminating evidence-based interventions such as Medication Treatment for opioid use disorder. Public health also involves interventions designed to address root causes of disease and poor health, including *social determinants of health*, which are factors such as poverty and inadequate access to health care. Public health research and clinical research go hand-in-hand to develop, evaluate, and disseminate effective interventions to reduce the burden of SUDs and to promote best health and recovery in a manner that is best suited for the needs of individuals and their communities.

Public Policy

Public policy refers to principles that serve as the foundation for organizational or governmental rules, regulations and laws that dictate individual and organizational behavior. The purpose of policy is to promote or dictate behaviors that benefit the public. In this chapter, we will focus on public policy as it relates to public health, specifically those policies that are designed to influence substance use behavior, treatment, and drug availability (i.e., drug policies). The development of public policies is complex and influenced by factors such as societal expectations and perceptions, economic goals, and political interest. Addiction psychiatrists can play an important role in shaping substance use treatment policies so that the policies are informed by research, in other words, that they are based on evidence. Policies that are developed based on scientific evidence, favor better health outcomes and are frequently referred to as "evidence based" policy [1]. This same approach is analogous to clinical treatments and interventions that are also based on scientific evidence of efficacy (shorter-term impact/health gain) and effectiveness (longer-term impact/health gain).

Prevention, public health, and public policy are interrelated and complementary approaches to reduce the burden of substance use and misuse and addiction rather than discrete, independent topics. Because stigma and discrimination against persons who use drugs are common and undermine prevention and public health treatment and recovery efforts, this chapter will also include brief discussion of stigma in health care settings. We also describe opportunities for clinician leadership in prevention, public health, and policy to reduce stigmatizing attitudes and policies that pose serious risk to effective treatment and recovery of persons suffering from SUDs.

Prevention

In a public health context, prevention is broadly defined as an activity or activities undertaken to reduce and eliminate the potential for a negative or worsening health outcome. We can conceptualize prevention activities working at different levels of health, including individual, family, community, and societal levels, where behaviors and contextual and environmental factors may shape substance use risk and set a course for dependence. Prevention efforts may include a wide variety of activities such as educational (e.g., classroom, peer, parenting), implementation of well-crafted public health policies, evidence-based interventions (e.g., school-based interventions to reduce adolescent depression or substance use) and effective behavioral and medication treatments that promote best health and reduce likelihood of progression to misuse or substance use disorder. Prevention activities may be undertaken by individuals themselves to improve their own health, or by others, including clinicians and their professional organizations. Prevention activities can also take place within a variety of settings, including clinical, educational, and community environments, to name a few. Prevention is conceptualized using the public health paradigm of "primary prevention," "secondary prevention," and "tertiary prevention"; however,

many prevention activities encompass aspects of these three categories affording an integrated approach to prevention versus considering only discrete categories.

Primary Prevention

Primary prevention includes activities that promote health and reduce the likelihood that individuals or groups will engage in risky substance use behaviors and/or reduce likelihood that experimentation with substance use among individuals or groups will progress to a substance use disorder. Primary prevention efforts frequently target youth in order to support early adoption of healthy behaviors for lifelong positive health outcomes.

Examples of primary prevention activities allow for understanding prevention at the individual level. Modalities of prevention at the individual level may include clinical intervention such as anticipatory guidance that a clinician provides to an adolescent or parent about youth experimentation with marijuana [8]. In this case, for an adolescent who has not experimented with marijuana or discloses limited experimentation, a prevention approach may include clinician use of motivational enhancement techniques (i.e., motivational interviewing) to elicit responses from the youth about reasons they consider important for abstaining from use or managing peer influence that supports their decision to abstain [8]. Interventions like *Project Chill* offer the primary care specialist the utility of a computer-based program that has been shown effective at lowering marijuana use among adolescents in urban health centers [12]. Another example of primary prevention could include clinician efforts to adopt opioid prescribing guidelines and pain management strategies that reduce the risk of a patient developing an opioid use disorder [12].

Additional primary prevention activities include group- or societal-level efforts such as public health policies that have demonstrated efficacy in reducing risky substance use behavior. For example, a well-studied policy approach with demonstrated efficacy to reduce adolescent alcohol-related harms includes laws that limit youth access to alcohol through age limits [12].

Secondary Prevention

Secondary prevention involves timely screening, diagnosis, and treatment of a disease or disorder. The objective in secondary prevention in addiction is diagnosis and treatment before progression to the life-threatening events [2]. Approaches to secondary prevention may include Screening, Brief Intervention, and Referral to Treatment (SBIRT) with populations who may be at heightened risk for substance use disorders, including those served at HIV care clinics. Expansion of access to treatment for substance use disorders (e.g., continuing medical education in clinical management of substance use and addiction and expanded third-party payer coverage) will also support secondary prevention efforts to screen and treat persons with substance use disorders [2].

Tertiary Prevention

Tertiary prevention involves managing and reducing the symptoms of chronic disease and co-occurring problems, including prevention of life-threatening adverse outcomes. An example of tertiary prevention includes providing naloxone to prevent death from opioid overdose to individuals who may or may not be receiving treatment for their substance use disorder [2, 6]. Provision of naloxone to others with whom individuals at risk for overdose live or spend time with is also an important part of supporting persons who are living with or in recovery from opioid use disorders. This can be expanded further by providing naloxone and appropriate training to law officers and emergency response personnel. Within tertiary prevention we may also consider relapse prevention and recovery support activities that can improve an individual's ability to manage their substance use disorder symptoms and related problems in order to achieve and maintain optimal health and well-being.

Prevention Through Harm Reduction

Harm reduction is a set of strategies, concepts, and approaches that are undertaken to reduce negative consequences of drug use including support for persons who actively use and are not ready to engage into treatment. An example of harm reduction is the evidence-based public health practice of making sterile syringes available to persons who inject drugs (e.g., heroin, cocaine, methamphetamine; cited by [12]. The significance of this single intervention is that it (a) reduces likelihood that the person who injects drugs will transmit or acquire a virus such as Hepatitis C or HIV, (b) respects the person's autonomy by leaving them in control of their use while offering treatment options and safer means to use, and (c) can meaningfully reduce stigma associated with injection drug use by providing a nonjudgmental environment where persons who are not yet ready to quit can more safely manage their use [12]. Sterile syringe exchange programs are a form of *primary prevention* in which providing sterile syringes reduces needle-sharing behavior and, which in turn, prevents the spread of blood-borne diseases. Since the person may already have a substance use disorder, then we could also consider a sterile syringe program as a *secondary prevention* approach when, for example, HIV or Hepatitis C testing and treatment are also provided. This same intervention could be considered *tertiary prevention* when the availability of sterile syringes is also reducing the likelihood that the individual's chronic condition (e.g., SUD or Hepatitis C) will be exacerbated by acquisition of yet another condition, such as HIV [12]. Harm reduction strategies such as provision of sterile syringes are a perfect example of the interrelatedness and overlap of primary, secondary, and tertiary prevention efforts.

Public Health

Public health is a multidisciplinary and interdisciplinary field that uses research, practice and policy approaches, strategies, methodologies, and interventions to promote best health and well-being at a population level. Public health is also devoted

to understanding and addressing societal, contextual, and environmental factors that undermine health and those factors that favor resilience, good health outcomes, and well-being. The Centers for Disease Control (CDC) and World Health Organization (WHO) characterize ten essential public health services that comprise the overarching roles and activities of the field of public health (https://www.cdc.gov/publichealthgateway/publichealthservices/pdf/ten_essential_services_and_sdoh.pdf). Following is a description of the ten essential public health services where we consider what each of them means in the context of substance use, misuse, and addiction. We then provide an overview of a public health strategy that has been used to reduce transmission of Hepatitis C in New York City [5].

Ten Essential Services of Public Health

On a global and national scale, there is general concordance in what constitutes public health services and corresponding activities. In each service category we provide an example of what this service would look like in a substance use or addiction context.

(1) *Surveillance* to monitor health indicators and identify and solve community health problems; (2) *Identify and investigate health problems* at a population level and propose action to reduce and eliminate the root causes of the problem as well as the problem itself; (3) *Health Promotion* to increase individual autonomy in making improvements in their own health, to protect health through service provision (e.g., availability of free or low-cost Hepatitis A vaccinations) and to provide timely and accurate information for educating the public about health issues that affect them, their families, and their communities; (4) *Disease Prevention* strategies and activities to prevent behaviors or conditions that lead to poor health outcomes (i.e., primary prevention), obtain screening and treatment (secondary prevention), or access to services that reduce worsening of chronic conditions, for example, access to sterile syringes for persons who inject drugs to prevent Hepatitis C or HIV acquisition (e.g., tertiary prevention); (5) *Community Mobilization and Engagement* to develop public health-community partnerships that can increase community responsiveness to and engagement, in solving public health problems; (6) *Policy Development* based on research and rigorous program evaluation to protect public health, including areas such protocols to prevent needle-stick injury among health professionals and Hepatitis A vaccination policies; (7) *Policy Enforcement* to promote compliance with national or state public health recommendations and laws such as mandatory prescriber and/or pharmacist registration in state Prescription Drug Monitoring Programs (PDMP); (8) *Linking the Public to Health Services* by promoting public knowledge about available services and increasing equitable access to public health services; (9) *Public Health Infrastructure* for development and maintenance of organizational service delivery structures and a sufficiently large and well-trained public health workforce to meet public health needs; and (10) *Research* for ongoing understanding of factors associated with health outcomes. Research includes prospective measurement of outcomes of interest (e.g., changes in types of drugs that contribute to overdose deaths in the United States over time), informing the

development of needed health information and interventions (e.g., scaling up availability of naloxone to prevent overdose deaths), and assessment of efficacy of current public health efforts and where improvements or changes may be needed (e.g., effectiveness of PDMP in reducing number of newly diagnosed cases of opioid use disorder).

Case Example: Public Health Strategy to Reduce Transmission of Hepatitis C in New York City [5]

Given that Hepatitis C virus (HCV) transmission in the United States is driven largely by lack of access to and low use of clean syringes and injection equipment among persons who inject drugs, public health efforts are well positioned to reduce and eliminate HCV transmission. Let us consider a public health approach using the ten-principle public health services to consider how HCV transmission can be reduced and stopped.

Public health *Surveillance* of new HCV cases (i.e., incidence) allows local, state, and national bodies to monitor changes in new cases over time as well as changes in HCV genotypes that may warrant changes in treatment protocols. By *identifying and investigating* HCV transmission, we are able to learn which populations are being disproportionately affected (e.g., persons who inject drugs, homeless individuals), reasons that contribute to transmission (lack of access to sterile injection equipment) and potential barriers to reducing HCV, including lack of available sterile syringe programs (SSP) (e.g., lack of political/social support for SSP and stigmatizing attitudes against persons who inject drugs). Effective *Health Promotion* efforts to reduce transmission include timely and accurate information about HCV prevention and treatment to educate key populations as well as efforts to reduce stigmatizing attitudes among clinicians and the public generally. In a systematic review of studies investigating stigmatizing attitudes among health care professionals, study authors found that some providers hold negative attitudes toward patients with SUD including perceptions that persons who use illicit substances may be violent, manipulative, or unmotivated [13]. The study also found that perceived discrimination from health care professionals has led to discontinuation of treatment among individuals with SUD [13]. *Disease prevention* strategies and activities to prevent behaviors or conditions that lead to transmission could include increased availability of SSP (i.e., primary prevention) and expanded testing and treatment for HCV among key populations (secondary prevention). *Community mobilization and engagement* to reduce HCV transmission include involvement of substance-using communities to provide recommendations on reducing their barriers to HCV treatment and related clinical care and services. Local, state, and national *policy development and enforcement* is needed to reduce barriers to availability of SSP and other effective public health measures (e.g., safe injection facilities) that could further reduce transmission and increase access to treatment. Activities that could increase access to treatment, *linking the public to health services*, could include, for example, outreach workers who can work with key populations in settings where they can be more effectively reached (e.g., street-based settings). Efforts to increase

public health infrastructure and workforce capacity could include educational efforts to reduce stigmatizing attitudes among clinicians and staff that may undermine treatment efficacy or adherence. *Research* can serve to inform the types of interventions that may be needed for specific subpopulations at risk for HCV, including efforts to promote optimal adherence to treatment for increasing successful HCV cure rate.

Conclusions

Public health approaches play a crucial role in reducing the societal burden of substance misuse and substance use disorders through integrated, multidisciplinary, and comprehensive approaches to substance use problems and importantly, the root factors that may contribute to development of problematic use and addiction. Clinicians are well positioned to play an important role in wider public health efforts through many avenues, including advocacy for policy changes and increased access to medication treatment.

Public Policy

Public policy refers to agency and governmental guidelines, regulations, and laws that are designed to influence behavior of individuals and groups to reduce negative health outcomes, societal problems, and costs to society. Policies can be regional, state, or federal, can change considerably over time, and span a broad spectrum of influences and contexts. For example, US clinical drug access and availability, access and availability of treatment for disorders, and laws that govern availability of substances or criminalize the possession or use of substances have changed substantially over time. In this section, we will focus on recent health policies that impact substance use treatment access and availability.

Substance Use Treatment Access and Expansion Policies

There are several federal laws that have influenced access to substance use disorder treatment. For example, the *Affordable Care Act 2010* [10] is a recent example of movement toward reforming health care as well as access to treatment for substance use disorders. In 2010, the Affordable Care Act was enacted by the US government to increase health insurance coverage for individuals, families, and small business owners. The Affordable Care Act also includes a provision on prevention, early intervention, and treatment of substance use disorders and mental health problems as an "essential health benefit" [10]. Another federal law designed to target substance use treatment is the *Mental Health Parity and Addiction Equity Act of* 2008 that requires insurance groups that provide health coverage to make benefits for substance use and/or mental health disorders no more restrictive than benefits offered for other medical care [10]. To address the growing and challenging concern

around underage drinking, the *Sober Truth on Preventing Underage Drinking Act (STOP Act)* of 2006 was authorized by the US federal government. Nationwide, the STOP Act provides additional funds to grantees under the Drug Free Communities Act of 1997 to prevent and reduce alcohol use among youth ages 12–20 years [10].

In the face of the opioid overdose epidemic in the United States, federal legislation, regulation, and guidelines for Opioid Treatment Program (OTP) and Medication Treatment (MT) (formerly Medication-Assisted Treatment [MAT]) have been developed. SAMSHA's Division of Pharmacologic Therapies (DPT), which is a part of SAMHSA Center for Substance Abuse Treatment (CSAT), together with the Drug Enforcement Administration (DEA) supervise the standard and certification process for OTPs and regulate certain medications used in MT [9]. The *Controlled Substance Act* governs medication used in MT and includes drug policy on regulation of manufacture, importation, possession, use, and distribution of controlled substances [9]. OTPs provide MT for individuals diagnosed with an opioid use disorder (OUD) with the goal of reducing, preventing, or eliminating use of illicit opioids (such as heroin) and provide safe and controlled level of medications like methadone, buprenorphine, and naltrexone to overcome the use of an abused opioid [11].

The *Drug Addiction Treatment Act of* 2000 *(DATA* 2000*)* gives permission for clinical practitioners to treat OUD with Schedule III, IV, and V medications or combinations of such medications that have received FDA approval for those conditions. This Act also allows physicians to obtain a waiver from the separate registration requirements of the *Narcotic Addict Treatment ACT* 1974 [9].

OTP regulations such as *Certification of Opioid Treatment Programs* and the 42 *Code of Federal Regulations (CFR) Part* 8 are behind the accreditation and certification of services for OTPs, with supervision from SAMSHA. It regulates use of narcotic drugs to treat opioid dependency [9]. 42 *CFR Part* 2 of the regulation protects patient confidentiality via restrictions in use and disclosure of patient information related to substance use treatment [9].

In 2015, *Federal Guidelines for Opioid Treatment Programs* were established. These guidelines help accrediting programs prepare for and meet accreditation standards for opioid treatment and also provide guidance and information on how programs can meet federal regulations and maintain compliance. The 2015 guidelines were an update from 2007 *Guidelines for the Accreditation of Opioid Treatment Programs* [9].

Access and Expansion Policies Related to Naloxone

The role of naloxone availability has received growing recognition from policymakers, public health advocates and clinicians alike. It is a prescription medication that reverses the effect of opioid overdose. In the United States, physicians and health care providers are able to prescribe naloxone to patients at risk of opioid overdose, including patients in treatment for opioid misuse or those who are taking high dose of prescription opioids for certain health conditions [4]. Expansion of availability to family and social networks of persons at risk for overdose allows for improved collective efforts to reduce unintended deaths due to opioid overdose [4].

In order to ensure safe and controlled distribution across the United States, all 50 states have approved naloxone access laws as of 2017 [3]. In many states, individuals most likely to respond to an overdose such as family, friends, harm reduction program staff, emergency medical technicians (EMTs), and law enforcement officers are able to obtain and administer naloxone under a variety of naloxone access policies [4]. In many states, naloxone access laws allow "third-party prescriptions," which are prescriptions issued to an individual who is not at risk of overdose but could use the drug on someone else to prevent overdose. Individuals who distribute, carry, and/administer naloxone, as per the law receive legal protection in nearly all the states in the United States [4]. Some states have also allowed physicians to sign standing orders for prescriptions for naloxone, thus further expanding access.

Conclusions

Substance-use-related public policies are broad in scope, and some will directly influence clinician prescribing behavior and patient access to treatment. Physicians and professional organizations are in a position to play a critical role in advocating for acceleration and adoption of public policies, as well as actively participating in the research process and public health efforts to reduce the burden of substance use disorders at individual, community, and societal levels.

This chapter was designed to expand the clinician's concept of substance use prevention and policy by introducing a public health perspective on substance use and related diseases. The chapter highlighted the various levels at which prevention efforts can take place (i.e., individual, community, policy) and the various points of intervention within each level. The public health perspective highlights how the integration and harmonization of epidemiological and health behavior findings can identify and leverage actions that can be taken by the clinician to reduce the societal burden of addiction. Finally, we present policy-level efforts at controlling use of and access to substances and how these efforts influence community- and individual-level factors. With this knowledge, we understand that substance use interventions require complementary and transdisciplinary approaches. A public health perspective highlights the complex landscape of substance use and comorbidities where clinicians, researchers, and policymakers can play significant roles to prevent, address, and reduce the burden of substance use, misuse, and addiction and intervene at key points throughout the course of addiction.

Review Questions

1. A 23-year-old female and her boyfriend present to your office seeking buprenorphine to treat her opioid use disorder. She reports that she is ready to start treatment and stop using heroin after she overdosed last week, and her boyfriend gave her naloxone nasal spray that he got from his methadone clinic. His methadone clinic has a weekly class on how to use naloxone sprays. She was taken to the emergency department after her overdose and revival with naloxone,

and was told about buprenorphine. Training individuals in the administration of naloxone is an example of _____ prevention.

A. Primary
B. Primary AND secondary
C. Secondary
D. Secondary AND tertiary
E. **Tertiary**

Explanation: For substance use disorders and addiction, preventing life-threatening adverse outcomes is tertiary prevention. Primary prevention is reducing the need to use substances, controlling access to substances, and promoting protective factors. Secondary prevention is diagnosing and treating substance use disorders.

Reference: Butler et al. [2]

2. As part of fellowship training, you tour emergency rooms, sober living environments, and syringe exchange services. During an encounter with a client exchanging syringes, she asks you who can carry naloxone. *Naloxone Access laws* passed in 2017 expanded access to naloxone for which of the following individuals?

A. ER physicians
B. Persons who inject opioids
C. Prison guards
D. **Family and close contacts of persons who inject opioids**
E. First responders

Explanation: In many states, expanded access to naloxone includes friends, family members, or lay and other professionals who work with individuals who are at risk for overdoes.

Reference: Prevention Solutions@EDC [4]

3. The director of your local public health department contacts you for advice on policy priorities to reduce opioid deaths in your region. Based on current science, which of the following would be the top policy or policies to target for greatest long-term decrease in opioid-related deaths?

A. Prescription monitoring program and acute pain prescribing practices
B. **Naloxone availability and medication treatment**
C. Prescription monitoring program and medication treatment
D. Acute and chronic pain prescribing practices
E. Drug reformulation and naloxone availability

Explanation: According to a study by Pitt et al. (2018) that undertook a mathematical modeling approach to assess relative benefits and potential harms of opioid-related policy responses, they found that policies that increased naloxone availability resulted in the greatest decrease in number of opioid deaths in the 11 interventions policy responses analyzed. This represented a 4% reduction in opioid overdose deaths.

Reference: Pitt et al. [7]

4. The city in which you are working is facing an outbreak of Hepatitis C among its young adult injection drug users. Considering the essential services, roles, and activities of public health, which of the following would be critical public health areas to develop in order to support an improved response to decreasing the transmission of Hepatitis C in this vulnerable youth population?
   A. **Surveillance, health promotion, and public health infrastructure**
   B. Surveillance, health promotion, and streamlining of federal funding
   C. Health promotion, public health media relations, and public health infrastructure
   D. Streamlining of federal funding, surveillance, and public health media relations

   Explanation: Among the critical public health approaches to curtailing this outbreak is surveillance and monitoring of cases, health promotion, and public health infrastructure. Surveillance will also one to track cases and observe increases or decreases in number of cases over time. Health promotion could include public awareness to increase secondary prevention to increase participation in screening for Hepatitis C. Health infrastructure can lead to increased clinician capacity to screen and treat.

   Reference: Laraque [5]
5. After one of your primary care colleagues' patients dies of overdose, she asks you if she can legally prescribe Buprenorphine. Which law allows for a waiver to prescribe narcotics for opioid use disorder?
   A. Sober Truth on Preventing Underage drinking Act (STOP Act) of 2006
   B. **Drug Addiction Treatment Act of 2000**
   C. Naloxone Access Law
   D. Mental Health Parity and Addiction Equity Act of 2008

   Explanation: As per SAMHSA's website, DATA 2000, part of the Children's Health Act of 2000, permits physicians who meet certain qualifications to treat opioid dependency with narcotic medications approved by the Food and Drug Administration (FDA)—including buprenorphine—in treatment settings other than OTPs.

   The Act permits qualified physicians to obtain a waiver from the separate registration requirements of the Narcotic Addict Treatment Act – 1974 (PDF | 437 KB) to treat opioid dependency with Schedule III, IV, and V medications or combinations of such medications that have been approved by the FDA for that indication.

   Reference: https://www.samhsa.gov/medication-assisted-treatment/statutes-regulations-guidelines

References

1. Brownson RC, Chriqui JF, Stamatakis KA. Understanding evidence-based public health policy. Am J Public Health. 2009;99(9):1576–83.

2. Butler JC. 2017 ASTHO president's challenge: public health approaches to preventing substance misuse and addiction. J Public Health Manag Pract. 2017;23(5):531–6.
3. DeSimone EM, Tilleman JA, Kaku KA, Erickson CT. Expanding access to naloxone. US Pharmacist. 2018;43(3):16–20.
4. Prevention Solutions@EDC and SAMHSA. Preventing the consequences of opioid overdose: understanding naloxone access laws. SAMHSA's Center for the Application of Prevention Technologies. [Internet]. 2018[cited 2019 June 26]; Available from: https://preventionsolutions.edc.org/sites/default/files/attachments/Preventing-Consequences-Opioid-Overdose-understanding-Naloxone-Access-Laws_0-1.pdf.
5. Laraque F, Varma JK. A public health approach to hepatitis C in an urban setting. Am J Public Health. 2017;107(6):922–6.
6. Peglow SL, Binswanger IA. Preventing opioid overdose in the clinic and hospital: analgesia and opioid antagonists. Med Clin North Am. 2018;102(4):621–34.
7. Pitt AL, Humphreys K, Brandeau ML. Modeling health benefits and harms of public policy responses to the US opioid epidemic. Am J Public Health. 2018;108(10):1394–400.
8. Ryan SA, Ammerman SD, Committee on Substance Use And Prevention. Counseling parents and teens about marijuana use in the era of legalization of marijuana. Pediatrics. 2017;139(3):e20164069.
9. SAMHSA. MAT statutes, regulations, and guidelines [Internet]. 2019 [cited 2019 May 17]. Available from: https://www.samhsa.gov/medication-assisted-treatment/statutes-regulations-guidelines.
10. SAMHSA. Laws and regulations [Internet]. 2019 [cited 2019 May 17]. Available from: https://www.samhsa.gov/about-us/who-we-are/laws-regulations.
11. SAMHSA. Medication and counseling treatment [Internet]. 2019 [cited 2019 May 17]. Available from: https://www.samhsa.gov/medication-assisted-treatment/treatment.
12. Chapter 5: Recovery: the many paths to wellness. In: Facing addiction in America: the surgeon general's report on alcohol, drugs, and health [Internet]. US Department of Health and Human Services; 2016 [cited 2018 Nov 16]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK424846/.
13. van Boekel LC, Brouwers EPM, van Weeghel J, Garretsen HFL. Stigma among health professionals towards patients with substance use disorders and its consequences for healthcare delivery: systematic review. Drug Alcohol Depend. 2013;131(1):23–35.

Ethical and Legal Considerations

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High-Yield Review Points

- The key ethical principles of beneficence, non-maleficence, respect for autonomy, and justice should guide the practice of addiction psychiatry.
- Everyday stigma faced by patients with substance use disorder can be magnified by stigma of medication-assisted treatment for opioid use disorders, and this can influence treatment access and retention.
- Current legal interventions to reduce overdose mortality in the United States include laws expanding access and availability to naloxone to help bystanders and/or first responders to reverse opioid overdoses.
- Regulatory frameworks under which opioid treatments have been delivered in the United States were marked by a period of limited regulation followed by a period marked by extreme regulation.
- Coordination and integration of primary care and substance use treatment must protect patient privacy using the general rule established by CFR 42 Part 2 and the HIPAA Privacy Rule.

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Introduction

Addiction psychiatry is a medical practice that manages substance use disorders with evidence-based clinical interventions. Ethics, stigma and discrimination, and legal discussions are presented using several examples from patients with opioid use disorders (OUDs) seeking medication treatment (MAT) as illustration. The approach to screening, assessment, and clinical care for patient with SUDs is based within the four principles of biomedical ethics. Any stigma or discrimination the patient has experienced due to their diagnosis should be addressed. Additionally, the practitioner should be informed of current regulatory frameworks that may guide implementation and utilization of treatment options. With this information in hand, the addiction psychiatrist will offer the best approach and information to address the patient's needs at the time.

Medical Ethics

Addiction psychiatry, like all clinical practices, often encounters difficult healthcare decisions. Beauchamp and Childress' principles of biomedical ethics allow us to question patient care and improve clinical decision-making for patients and their families [1]. The four basic principles of biomedical ethics are: (1) beneficence, (2) non-maleficence, (3) respect for autonomy, and (4) justice. Many readers may be familiar with these principles in the clinical research context, particularly as they discuss informed consent when enrolling or referring patients into trials. Additionally, physicians must build trust with their patients and have a fiduciary duty to protect information [2]. These principles should also guide daily patient care.

The principle of beneficence requires the physician's intent of doing good for the patient (i.e., tailoring care to avoid additional burdens for the patient). Non-maleficence explicitly requires the physician do no harm to the patient. Respect for autonomy ensures the patient's decision-making process in enrolling in or denying substance use treatment is free of coercion. To help respect a patient's autonomy, it is important to fully explain the risks and benefits of all treatment options so they can make an informed decision. The principle of justice requires that treatment options are fair to all patient populations and that they remain in compliance with federal and state regulations. Finally, physicians are also responsible for social and political advocacy to improve substance use treatment resources in order to improve patient health.

Clinical settings with substance use disorders can rely upon ethical principles to ensure patients understand the physical and legal implications of their diagnosis and treatment options. It is challenging to apply the non-maleficence principle when the treatment itself will allow a patient with an opioid use disorder to experience opioid withdrawal; however, one can rely on the principle of beneficence to explain the net benefit of medication-assisted treatment (MAT) for this patient. Together, the patient and the addiction psychiatrist can use ethical principles to discuss the physical (e.g., side effects) and psychosocial risks (e.g., stigma, discrimination), as well as the benefits, when they tailor treatment plans. By doing so, the patient will be fully informed

and know the implications of agreeing to start a treatment regimen. Physicians must uphold the principle of respect for autonomy when physician and patient goals differ. For example, a physician may insist on methadone as the optimal treatment to reduce the risks associated with a patient's opioid use disorder, including overdose and death. However, if the patient's competing priorities place more value on their quality of life and is expressing concern over methadone clinics, the physician can respect the patient's autonomy and offer pros and cons on alternative treatments such as buprenorphine, naltrexone, or non-pharmacologic treatments.

Using the principle of justice, the addiction psychiatrist can help ensure fair distribution of treatment resources among patient populations with substance use disorders. For example, one should ensure that if medication options like buprenorphine and methadone are equally available in their clinical setting, they should be equally available to all patients with opioid use disorder regardless of gender, race, or ethnicity. This principle must be used with the principle of non-maleficence to ensure the optimal dosing for each treatment option. This is particularly important since methadone under-dosing is more common among programs serving high proportions of African-American patients, raising critical concerns in care delivery to reduce racial disparities [3]. Please refer to Part III, Chap. 18, for additional information on treatment disparities among underserved populations.

Informed consent includes a discussion with the patient to address concerns and confirm the knowledge guiding their decision to participate or not participate in substance use treatment. To protect the patient and others from harm, the addiction psychiatrist should be aware that they may need to balance the respect for autonomy of a person with impaired judgment, alongside obligations of beneficence, non-maleficence, and justice. One should be prepared to revisit informed consent discussions and document them as part of the medical record as the patient's clinical presentation and decisions change. Using the principle of respect for autonomy, one should recognize that a signed consent to treatment is not equivalent to an informed consent. Given the complexities of multifaceted MAT programs, patient consent to start a treatment plan requires a carefully documented patient orientation on treatment options and requirements [4]. To give an informed consent, the patient must know and understand the benefits and consequences of enrolling in MAT. A transparent approach to consenting to treatment will include full disclosure of all procedures involved in MAT, recordkeeping of personal data and confidentiality (i.e., networks with access to that data, divulging information without additional consent), involuntary discharge procedures, and facility safety instructions [4].

Stigma and Discrimination

Stigmatized persons are often labeled by an individual trait or characteristic that culturally devalues them [5]. Link and Phelan describe status loss and discrimination as the consequences of stigma when a person is labeled with an undesirable characteristic [5]. Consequently, discrimination of persons with substance use disorders will lead to unequal treatment outcomes [6]. Patients may be facing double stigma related to seeking MAT and to the underlying substance use disorder, which may

produce exclusion from social and economic life [7, 8]. Discrimination and stigma related to substance use may be a complex barrier to accessing and receiving treatment [9–11], and is associated with poorer physical and mental health [12]. Stigma can be enacted by different people, including healthcare providers, and experienced differently by different types of patients, but it can be modifiable [8, 13]. In order to minimize stigma and discrimination for persons with substance use disorders, it is important to treat patients with compassion, respect, and dignity regardless of substance use career, race, age, gender, disabilities, or sexual orientation [6].

MAT-related stigma can be driven by different attributes in the substance use patient. Stigma can also affect the internal operation of MAT programs when healthcare staff absorb society's MAT-related stigma and deliver services with punitive behavior. For example, some factors associated with increased stigma among methadone patients have been previously described as concurrent drug use, co-occurring psychiatric disorders (e.g., anxiety, depression), self-reported positive HIV status, current pain or discomfort, a previous history of substance use treatment, and higher education (i.e., attended college) [14, 15]. When addressing patient questions related to starting treatment, it would be helpful to probe for MAT-related stigma concerns (e.g., job discrimination, worries about swapping one drug for another) and take the time to address any negative thoughts or feelings that could diminish the patient's self-image resulting from starting MAT. Leadership, supervision, and educational efforts can help improve attitudes toward persons in MAT [4].

Addictions and the Law

Internationally, drug policies vary widely based on the nation's approach to reduce drug production, trafficking, and consumption. The United States maintains a criminal justice approach to drug laws rather than a health-oriented approach. Drug control efforts in the United States have traditionally focused on international eradication of product, trafficking suppression, and criminalizing consumers. Despite this drug policy approach, overdose deaths in the United States, driven by synthetic opioids (other than methadone), continue to increase significantly [16]. Therefore, the United States declared a national public health emergency to address the national opioid overdose crisis to improve "prevention, treatment, and recovery support services" and improve opioid prescribing practices, among other strategies to reduce opioid use [17]. Meanwhile, other countries have moved toward regulating drug consumption while improving access to substance use treatment. For example, in 2001, Portugal introduced Law 30/2000 to decriminalize personal drug use, ending penal sanctions for possession, and rapidly expanded the provision of evidence-based treatment, which led to significant reductions in drug-related deaths [18].

A history of tough sentencing rules for drug violations has exacerbated racial disparities in the criminal justice system in the United States. For example, the Rockefeller Drug Laws in New York State in 1973 raised criminal penalties for the sale and possession of drugs, primarily heroin. But an ambiguity in the law permitted discretionary exceptions that would allow for those being arrested to come primarily from black and Latino neighborhoods [19]. More than 6.6 million persons

are currently under the supervision of US adult correctional systems and have been shown to have unmet healthcare needs and high rates of substance use disorders [20]. Different models for linking persons with substance use disorders at several stages of the criminal justice system process into detoxification management and substance use treatment for alcohol and opioids can be found in Chap. 18.

Other legal interventions that can help expand access to substance use treatment are the expansion of Medicaid to provide coverage for previously uninsured Americans. Following the Affordable Care Act (ACA) in 2008 and the 2012 Supreme Court's decision on Medicaid expansion, US states decided whether to adopt the Medicaid expansion for most low-income adults to 138% of the federal poverty level. As of 2018, 34 states including the District of Columbia had approved Medicaid expansion [21]. However, there is a need to repeal the Medicaid "inmate exception" and reform reimbursement for substance use treatment inside correctional systems [22].

Using the principle of justice, many leaders have called for drug policy reforms to prevent the harms associated with substance use. The criminalization of consumers in US drug policy has evolved to public health efforts aimed at reducing overdose and blood-borne infections driven by substance use. Resistance to needle-exchange programs persists in most states, and the Department of Justice is threatening criminal prosecution for those involved in supervised injection facilities [23]. Current legal interventions to reduce overdose mortality in the United States include expanding naloxone access to help bystanders and/or first responders to reverse opioid overdoses. All 50 states and the District of Columbia have modified their laws to increase access to naloxone, which aids in reducing liability fears for those prescribing or dispensing naloxone [24]. Additionally, some states have passed overdose Good Samaritan laws to protect bystanders from arrest or prosecution when they report an overdose in good faith [24].

Medical Licensure and Credentialing in Addiction Psychiatry

Addiction psychiatrists should be aware of the regulatory frameworks under which opioid agonist treatments have been delivered in the United States. Before the Harrison Narcotic Tax Act of 1914, there was a period of limited regulation favoring the clinical independence of individual providers, which was followed by a period marked by extreme regulation. The Harrison Narcotics Tax Act, introduced to implement a treaty obligation to regulate the manufacture and trade of opioids, contained a clause relating to the medical use of narcotics that the Supreme Court interpreted as prohibiting the prescription of narcotics to habitual users on the grounds that addiction was not a disease [25, 26]. Later cases, particularly *Linder v. United States* in 1925, essentially reestablished the right of a physician to prescribe opioids to a patient in her direct care on the basis that such behavior amounted to the exercise of "professional conduct with which Congress never intended to interfere." [27] However, by this time opioid agonist treatment was limited to a very small number of specialized clinics.

In 1958, a joint committee of the American Bar Association and the American Medical Association recommended trials of opioid agonist treatment in outpatient

settings [4]. Later, the Controlled Substances Act of 1970 required registration with the Drug Enforcement Administration (DEA) for prescribing, dispensing, and administering controlled substances. As support for treatment options continued to grow, Congress amended the Controlled Substances Act with the Narcotic Addict Treatment Act of 1974. This Act brought several changes and improved coordination between the US Department of Health and Human Services (DHHS) and the DEA. It established the National Institute on Drug Abuse (NIDA) independently from the National Institute on Mental Health, and split opioid treatment regulation between NIDA (responsible for treatment standards) and the Food and Drug Administration (FDA; responsible for safety, effectiveness, and approval of new drugs for treatment). The Narcotic Addict Treatment Act defined maintenance treatment in federal law and required separate DEA registration for dispensing opioids for opioid use disorder treatment. Therefore, a physician would no longer be able to prescribe methadone for OUD without additional registration. Once the DHHS determined a medical practitioner was qualified based on treatment standards established by NIDA, they could apply for and obtain registration from the DEA [4]. Outpatient methadone treatment can only be provided by Opioid Treatment Programs (OTPs), which are registered by the DEA and certified at the federal level by Substance Abuse and Mental Health Services Administration (SAMHSA) [4, 28]. OTPs can include outpatient, intensive outpatient, residential, and hospital settings, which are in conformance with Title 42 of the Code of Federal Regulations Part 8 (CFR Part 8) [4, 29].

The Drug Addiction Treatment Act (DATA 2000) amended the Narcotic Addict Treatment Act by allowing physicians to obtain a waiver from separate registration requirements for Schedule III, IV, and V medications approved by the FDA to treat opioid use disorder. However, physicians (MD or DO; and later nurse practitioners and physicians' assistants) must meet certain qualifications under DATA provisions that include state license, DEA registration, certification/training for treatment and management of opioid use disorders, treat a maximum of 30 patients within the first year, and have the capacity to refer patients to counseling and ancillary services [4, 30]. Given that DATA 2000 does not disqualify practitioners in residency programs, SAMHSA grants waivers to those with unrestricted licenses and DEA registration [30]. In 2002, the FDA-approved buprenorphine for opioid use disorder treatment and for supervised withdrawal, which allowed physicians with the waiver in non-opioid treatment program settings to prescribe to patients. In 2013, modifications to 42 CFR Part 8 allowed buprenorphine products to be dispensed without adhering to a time in treatment [29].

Privacy Laws in the Context of Addiction Psychiatry

Guided by the principles of beneficence and non-maleficence, the addiction psychiatrist may need to disclose patient information about substance use treatment to improve coordination and integration of primary care and substance use treatment. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule (45 CFR Parts 160 and 164) sets limits and conditions on the uses of personal health information and patient medical records without patient consent [31]. If a

substance use treatment program (including individual providers and provider organizations) transmits health information in an electronic form (e.g., inquiry of eligibility to health plans, submission of claims) it is considered a covered entity and they must comply with the Privacy Rule. Under the Privacy Rule, a program may not use or disclose protected health information, which includes information that may identify a patient such as medical record numbers and employment information [31].

As previously mentioned, stigma related to substance use disorders may act as a barrier to seek or stay in treatment. Therefore, Congress moved to improve confidentiality laws and extend legal protection to substance use treatment records in the 1970s. This set of healthcare regulations are known as Title 42 of the Code of Federal Regulations Part 2 (42 CFR Part 2) [31], or Part 2. Part 2 ensures that a patient does not face adverse consequences related to criminal and domestic proceedings because they are receiving substance use treatment. Part 2 prohibits disclosing any information that could identify a patient as having a history of substance use without written consent. Part 2 and the HIPAA Privacy Rule have different general rules regarding the use of patient health information. Substance use programs will not disclose information without consent or identify an exception to the rule in Part 2 that allows disclosure and ensure that it is permitted by the Privacy Rule [31]. For example, Part 2 allows programs to report limited information to law enforcement on crimes that occur on program premises, including patient name and address [31]. Part 2 will also allow programs to release information in response to a subpoena if the patient provides written consent, which will also comply with the Privacy Rule qualified protective order [31]. Providers are also required by law to report child abuse and neglect to local authorities [4]. It is important to identify if the type of setting the provider is in, and if Part 2, HIPAA Privacy Rule, or both apply. The Office of the National Coordinator (ONC) for Health Information Technology and the SAMHSA offer technical guidance to help stakeholders understand how Part 2 applies in complex healthcare settings.

Review Questions

1. A 47-year-old African-American male who works 6 days a week in construction and a 23-year-old female Latinx patient both present to an opioid treatment program seeking maintenance treatment for their opioid use disorder. Which of the following principles of biomedical ethics is most likely to be used when offering treatment options equally among patients with substance use disorders?
   A. Beneficence
   B. Justice
   C. Non-maleficence
   D. Insurance

   Correct answer: B. Justice. Justice is the medical ethical principle that requires that treatment options are fair to all patient populations and that they remain in compliance with federal and state regulations. Beneficence and non-maleficence

are other medical ethical principles unrelated to equity of treatment. Insurance is a distracting answer, and not a medical ethical principle.

2. A 35-year-old female construction worker residing in a suburban area is unable to commute to the methadone OTP for her opioid use disorder. She found a general medicine practitioner who is authorized to prescribe buprenorphine in a local community clinic. Which of the following legislations allowed physicians (MD or DO; and later nurse practitioners and physicians' assistants) to obtain a waiver from separate registration requirements for Schedule III, IV, and V medications approved by the FDA to treat opioid use disorders?
   A. Narcotic Addict Treatment Act of 1974
   B. Harrison Narcotics Tax Act of 1914
   C. Drug Addiction Treatment Act of 2000
   D. Affordable Care Act of 2010

   Correct answer: C. The Drug Addiction Treatment Act (DATA 2000) amended the Narcotic Addict Treatment Act by allowing physicians (MD or DO; and later nurse practitioners and physicians' assistants) to obtain a waiver from separate registration requirements for Schedule III, IV, and V medications approved by the FDA to treat opioid use disorder. The Harrison Narcotics Tax Act of 1914 does not regulate the clinical independence of individual providers. The Affordable Care Act of 2010 is a distracting answer.

3. A 27-year-old male fast food worker is concerned he may not make his shift on time if he starts methadone maintenance treatment for his opioid use disorder. He fears he may be fired from his job and questions would arise if he requests a later start time. Which of the following consequences of stigma should be addressed when probing for patient concerns regarding treatment?
   A. Positive stereotypes
   B. Improved self-image
   C. Status loss and discrimination
   D. Acceptance and impartial treatment

   Correct answer: C. If the patient's employer finds out he needs a later start time to start treatment for an opioid use disorder, they will know he is using opioids. Link and Phelan describe status loss and discrimination as the consequences of stigma when a person is labeled with an undesirable characteristic. Positive stereotypes, improved self-image, acceptance, and impartial treatment are the opposite of experiences related to stigma.

4. An 18-year-old female with a history of heroin injection drug use recently completed a residential treatment program. When returning home, she used her regular heroin dose and experienced an overdose. Fortunately, her parent called 911 and first responders arrived in time to reverse the overdose. Which of the following legal interventions have helped reduce opioid overdoses in the United States?
   A. Expansion of naloxone access
   B. Rockefeller Drug Laws in New York State in 1973

C. Title 42 of the Code of Federal Regulations Part 2
D. Law 30/2000

Correct answer: A. The expansion of naloxone access has directly reduced opioid overdoses by increasing the availability of an overdose reversal drug in the community. Rockefeller Drug Laws raised criminal penalties for the sale and possession of drugs, primarily heroin. Part 2 is a distracting answer, and is related to privacy laws. Law 30/2000 has helped reduce opioid overdoses in Portugal.

5. A 39-year-old male with 5 years of methadone maintenance treatment recently lost insurance coverage. If a substance use treatment program is subject to both 42 CFR Part 2 and HIPPA Privacy Rule, can they disclose a medical record number to obtain authorization for referring an individual to another healthcare provider?
   A. Yes, the medical record number can be used to identify the patient by sources external to the program.
   B. Yes, even though the medical record number can identify the patient, it is important to not delay the referral while waiting for patient consent.
   C. No, a medical record number is considered protected health information.
   D. No, one must contact legal counsel for assistance before reaching a decision.

   Correct answer: C. Under the Privacy Rule, a program may not use or disclose protected health information, which includes information that may identify a patient such as the medical record number. The other options are distracting answers.

References

1. Beauchamp TL, Childress JF. Principles of biomedical ethics. 7th. ed. New York: Oxford University Press; 2012.
2. Dickens BM, Cook RJ. Law and ethics in conflict over confidentiality? Int J Gynecol Obstet. 2000;70(3):385–91.
3. D'Aunno T, Park S, Pollack HA. Evidence-based treatment for opioid use disorders: a national study of T methadone dose levels, 2011–2017. J Subst Abuse Treat. 2019;96:18–22.
4. U.S. Department of Health and Human Services. Medication-assisted treatment for opioid addiction in opioid treatment programs. Treatment Improvement Protocol (TIP) series 43. DHHS publication no. (SMA) 05-4048. Substance Abuse and Mental Health Services Administration: Rockville; 2005.
5. Link BG, Phelan JC. Conceptualizing stigma. Annu Rev Sociol. 2001;27(1):363–85.
6. American Association for the Treatment of Opioid Dependence (AATOD). Canon of Ethics [Internet]. AATOD. 2019. [cited 2019 May 10]. Available from: http://www.aatod.org/member-center/canon-of-ethics/.
7. Parker R, Aggleton P. HIV and AIDS-related stigma and discrimination: a conceptual framework and implications for action. Soc Sci Med. 2003;57(1):13–24.
8. Smith LR, Earnshaw VA, Copenhaver MM, Cunningham CO. Substance use stigma: reliability and validity of a theory-based scale for substance-using populations. Drug Alcohol Depend. 2016;162:34–43.

9. Skinner N, Feather NT, Freeman T, Roche A. Stigma and discrimination in health-care provision to drug users: the role of values, affect, and deservingness judgments. J Appl Soc Psych. 2007;37(1):163–86.
10. Deering DE, Sheridan J, Sellman JD, Adamson SJ, Pooley S, Robertson R, Henderson C. Consumer and treatment provider perspectives on reducing barriers to opioid substitution treatment and improving treatment attractiveness. Addict Behav. 2011;36(6):636–42.
11. Lago RR, Peter E, Bógus CM. Harm reduction and tensions in trust and distrust in a mental health service: a qualitative approach. Subst Abuse Treat Prev Policy. 2017;12(1):12.
12. Ahern J, Stuber J, Galea S. Stigma, discrimination and the health of illicit drug users. Drug Alcohol Depend. 2007;88(2):188–96.
13. Kulesza M, Larimer ME, Rao D. Substance use related stigma: what we know and the way forward. J Addict Behav Ther Rehabil. 2013;2(2):2–6.
14. Tran BX, Vu PB, Nguyen LH, et al. Drug addiction stigma in relation to methadone maintenance treatment by different service delivery models in Vietnam. BMC Public Health. 2016;16(1):238.
15. Luoma JB, Twohig MP, Waltz T, et al. An investigation of stigma in individuals receiving treatment for substance abuse. Addict Behav. 2007;32(7):1331–46.
16. Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G. Drug and opioid-involved overdose deaths – United States, 2013–2017. Morb Mortal Wkly Rep. 2019;67(5152):1419–27.
17. U.S. Department of Health and Human Services. HHS acting secretary declares public health emergency to address national opioid crisis. 2017. [cited 2019 May 10]. Available from: https://www.hhs.gov/sites/default/files/opioid%20PHE%20Declaration-no-sig.pdf.
18. Hughes CE, Stevens A. What can we learn from the Portuguese decriminalization of illicit drugs? Br J Criminol. 2010;50(6):999–1022.
19. National Institute of Law Enforcement and Criminal Justice. The Nation's toughest drug law: evaluating the New York experience – final report of the Joint Committee on New York Drug Law Evaluation. New York: The Association of the Bar of the City of New York; 1978.
20. Kaeble D, Cowhig M. Correctional populations in the United States, 2016. U.S. Department of Justice, Office of Justice Programs, Bureau of Justice Statistics. 2018; NCJ 251211:1–13. [cited 2019 May 10]. Available from: https://www.bjs.gov/content/pub/pdf/cpus16.pdf.
21. Kaiser Family Foundation. Status of state action on the medicaid expansion decision [Internet]. KFF State Health Facts. 2018. [cited 2019 May 10]. Available from: https://www.kff.org/health-reform/state-indicator/state-activity-around-expanding-medicaid-under-the-affordable-care-act.
22. Fiscella K, Beletsky L, Wakeman SE. The inmate exception and reform of correctional health care. Am J Public Health. 2017;107(3):384.
23. Gostin LO, Hodge JG, Noe SA. Reframing the opioid epidemic as a national emergency. JAMA. 2017;318(16):1539–40.
24. Network for Public Health Law. Legal interventions to reduce overdose mortality: naloxone access and overdose good Samaritan Laws. Network for Public Health Law (USA); 2018 [cited May 10, 2019]. Available from: https://www.networkforphl.org/_asset/qz5pvn/legal-interventions-to-reduce-overdose.pdf.
25. Harrison Narcotics Tax Act. Public law # 63–223. 1914.
26. Webb v. United States, 249 U.S. 96, 39 S. Ct. 217, 63 L. Ed. 497. 1919.
27. Linder v. United States, 268 U.S. 5, 45 S. Ct. 446, 69 L. Ed. 819. 1925.
28. U.S. Food and Drug Administration. Methadone oral concentrate (methadone hydrochloride oral concentrate USP) and methadone sugar- free oral concentrate (methadone hydrochloride oral concentrate USP) dye-free, sugar-free, unflavored. [cited 2019 May 10]. Available from http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/017116s021lbl.pdf.
29. Opioid Drugs in Maintenance and Detoxification Treatment of Opiate Addiction. Proposed modification of dispensing restrictions for buprenorphine and buprenorphine combination as used in approved opioid treatment medications. 42 C.F.R. § 8.12 (2016) [regulation on the Internet]. [cited 2019 May 10]. Available from: https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=e3d2eafa3a0991f90e93a038912a687e&mc=true&n=pt42.1.8&r=PART&ty=HTML#sp42.1.8.c.

30. U.S. Department of Health and Human Services. Qualify for a practitioner waiver [Internet]. Substance Abuse and Mental Health Services Administration. 2019. Available from: https://www.samhsa.gov/medication-assisted-treatment/buprenorphine-waiver-management/qualify-for-practitioner-waiver.
31. CSAT (Center for Substance Abuse Treatment). The confidentiality of alcohol and drug abuse patient records regulation and the HIPAA privacy rule: implications for alcohol and substance abuse programs. DHHS publication no. (SMA) 04-3947. Substance Abuse and Mental Health Services Administration: Rockville; 2004. https://www.integration.samhsa.gov/operations-administration/the_confidentiality_of_alcohol_and_drug_abuse.pdf.

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