

SUBSTANCE-RELATED AND ADDICTIVE DISORDERS

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Mind-altering substances (psychoactive drugs¹) have been a part of human life for at least 10,000 years (Sullivan & Hagen, 2002). Evidence of drug use begins as early as 8000 BC when humans began to chew the betel nut for its stimulating effects (Gorman, 1970) and drink mead wine (McGovern et al., 2004). Since then, humans have continuously used mind-altering substances for religious, medicinal, and recreational purposes (Crocq, 2007). Only in the past century has attention turned toward problematic drug use (Beckett, 1994), accompanied by legal measures to impede access to certain drugs (Reuter, 1992). However, such legal efforts have proven largely ineffective (e.g., Miron & Zwiebel, 1991).

Today, most adults report consuming drugs at some point in their lives, suggesting that casual use remains quite common (Substance Abuse and Mental Health Services Administration [SAMHSA], 2015). However, a subset of individuals develop substance use disorders (SUDs)—complex, chronic, and relapsing psychiatric conditions (McLellan, Lewis, O'Brien, & Kleber, 2000) with staggering physical, economic, and social costs. Although individuals with SUDs constitute a relatively small proportion of casual drug users, they also represent the most common of psychiatric disorders, with a lifetime prevalence of 35.3% (National Institute of Mental Health, 2007). In this chapter, we begin by briefly describing

substance-related and addictive disorders as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed., or *DSM-5*; American Psychiatric Association, 2013). We focus on SUDs specifically and discuss their prevalence, demographics, comorbidity, and risk factors. Then, we review neurobiological and psychological models of drug use and addiction, consider the role of craving, and conclude with a review of prominent treatment approaches.

DEFINITIONS AND DIAGNOSTIC CRITERIA

The “Substance-Related and Addictive Disorders” chapter in *DSM-5* establishes standardized diagnostic criteria for disorders related to substance use, including SUDs, and substance-induced disorders (e.g., substance intoxication, withdrawal). This chapter focuses on SUDs. Within this category, a separate SUD is defined for each specific drug or drug class (i.e., alcohol; tobacco; cannabis; cocaine; amphetamines; phencyclidine; hallucinogens; opioids; sedatives, hypnotics, and anxiolytics; inhalants; and other or unknown substances). This separation is important because each drug is associated with a unique primary mechanism of action (Pierce & Kumaresan, 2006), producing characteristic pharmacological, neurological, and psychological effects.

¹Psychoactive drugs are those that primarily act on the brain and change thinking, mood, and behavior. They include legal drugs (e.g., alcohol, nicotine, caffeine, and opioid pain medications) and illicit drugs (e.g., heroin, cocaine, amphetamines, and marijuana).

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Nevertheless, there are also commonalities across drugs, including their ability to reinforce behavior and induce intoxication, tolerance, and withdrawal symptoms upon cessation of use. Therefore, the criteria for each SUD are based on a similar underlying structure.

To be diagnosed with SUD, an individual must report problematic drug use with significant impairment or distress, accompanied by at least two of the following 11 symptoms:

1. using greater amounts of the drug than intended;
2. failing to quit or control drug use despite the desire to do so;
3. spending substantial time on drug-related activities;
4. craving the drug;
5. failing to fulfill major responsibilities at work, school, or home;
6. continuing drug use despite social problems;
7. giving up other activities because of drug use;
8. using drugs in physically risky situations;
9. continuing drug use despite physical or psychological problems;
10. showing signs of tolerance (need for increasing amount to achieve intoxication); and
11. showing signs of withdrawal (for details, see American Psychiatric Association, 2013).

Conceptually, these symptoms can be grouped into subcategories of impaired control over drug use (Symptoms 1–4), risky use (5–6), social impairment (7–9), and physical dependence (10–11). However, severity is determined across categories, based on the number of symptoms endorsed. That is, endorsement of any two symptoms qualifies for a diagnosis of mild SUD; endorsement of four to five symptoms, moderate SUD; and endorsement of six or more, severe SUD. Importantly, craving for substances is a new diagnostic criterion in *DSM–5*, reflecting the accumulation of evidence linking craving to increased drug use and relapse (see below for discussion). This modification also increased concordance in diagnoses between the *DSM–5* and the current edition of the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*

published by the World Health Organization (1992), which also includes craving as a criterion for (substance) dependence syndromes. Notably, SUDs are closely associated with the concept of addiction, defined elsewhere as “a primary, chronic disease of brain reward, motivation, memory, and related circuitry” (American Society of Addiction Medicine, 2011, para. 1).

DSM–5 now includes gambling disorder (GD) in a new category of behavioral addictions. GD was reformulated from pathological gambling, which was included in the compulsive disorders category in the fourth edition of the manual. This change in category was motivated by evidence that pathological gambling involved features similar to SUDs in terms of behavioral expression and underlying neurobiology (Leeman & Potenza, 2012). For example, individuals with pathological gambling exhibited continued use despite negative consequences and experienced loss of control, craving (gambling urges), and phenomena that resemble tolerance and withdrawal. Because GD is a new diagnosis, few studies have been published since its inclusion in *DSM–5*, precluding systematic review; we hope that such data will become available for future versions of this chapter. Internet gaming is another behavior that may share features of SUD; for now, it has been placed in a special category, to be considered for inclusion in future editions of *DSM*, pending additional evidence (Petry & O’Brien, 2013).

It is important to note that across both SUDs and GD, individuals who endorse distinct subsets of symptoms would still qualify for the same diagnosis (i.e., there are 2,036 possible combinations of symptoms). As such, the current diagnostic system disregards possible SUD subtypes, even within a single drug. Furthermore, SUD and GD diagnoses are based on reportable symptoms, rather than on the underlying neurobiology (as with other psychiatric disorders). These issues may be addressed in the future by the Research Domain Criteria initiative, which aims to integrate multiple levels of analysis to better understand basic dimensions of functioning and their underlying pathophysiology (rather than diagnostic categories; Insel et al., 2010).

PREVALENCE, DEMOGRAPHICS, AND COMORBIDITY

SUDs are the most prevalent psychiatric conditions in the United States,² estimated to affect 35% of adults at some point in their life (National Institute of Mental Health, 2007), many of whom are polysubstance users (SAMHSA, 2015). In 2014, approximately 20.2 million people in the United States age 18 years or older (8.4%) reported an active SUD involving alcohol or drugs other than nicotine (SAMHSA, 2015). Tobacco–nicotine use disorder affects an estimated 30.6 million adults, or 12.7% of U.S. adults (Centers for Disease Control and Prevention [CDC], 2015a; SAMHSA, 2015). These figures are striking and highlight the widespread prevalence of SUDs. However, the rates of casual drug use are even greater. For example, in 2014, although 20.2 million individuals reported an SUD (except tobacco), an additional 190.2 million reported using drugs without meeting the criteria for an SUD (SAMHSA, 2015). This discrepancy suggests that some individuals are at greater risk for escalation of drug use, and others can maintain casual use without developing an SUD (see Risk Factors section).

Because they are so prevalent, drug use and SUDs are associated with staggering social and economic societal-level costs. For example, cigarette smoking is the leading preventable cause of disease and death in the United States, accounting for at least 480,000 deaths annually (B. D. Carter et al., 2015; SAMHSA, 2014), or nearly one in five deaths (Xu, Murphy, Kochanek, & Bastian, 2016). Alcohol is the fourth preventable cause of death, accounting for approximately 88,000 deaths annually (Stahre, Roeber, Kanny, Brewer, & Zhang, 2014). In 2014, drug overdoses were responsible for 47,055 deaths (CDC, 2015b), including 5,415 deaths due to cocaine, 10,574 deaths due to heroin, and 25,760 specifically due to prescription drugs (e.g., prescription opioid pain drugs; CDC, 2016). Notably, the mortality rate for prescription opioid medications have more than

quadrupled since 1999 and it is now considered the nation's fastest growing drug problem and an epidemic (CDC, 2016; National Drug Intelligence Center, 2013). Other health-related costs include those associated with infectious diseases: Needle sharing and unprotected sex associated with drug use can lead to HIV, hepatitis, and other diseases (Mathers et al., 2008). Importantly, legality of a drug does not guarantee safety. For instance, cigarette smoke contains toxic compounds, many of which are carcinogenic and known to damage almost every organ system, contributing to a variety of chronic diseases (SAMHSA, 2014). Consistently, cigarette smoking, which is legal, accounts for 3 times as many deaths as alcohol and all illicit drugs combined, and more than 20 times as many deaths as illicit drugs alone (CDC, 2016; SAMHSA, 2014).

Economically, annual U.S. expenditures for drug-related costs due to crime, accidents, lost productivity, and health care are estimated at more than \$700 billion. Of those, more than \$289 billion relate to tobacco cigarettes (SAMHSA, 2014), \$223.5 billion to alcohol (Bouchery, Harwood, Sacks, Simon, & Brewer, 2011), and approximately \$193 billion to illicit drug use (National Drug Intelligence Center, 2011). Other social costs include lower academic performance (Cox, Zhang, Johnson, & Bender, 2007; Singleton & Wolfson, 2009) and higher rates of student drop out (Ellickson, Tucker, & Klein, 2001), which can lead to additional costs at the societal level.

Although SUDs are reported across age, sex or gender, race, and economic status, certain demographic trends are apparent. For example, rates of past-year SUDs are higher in males compared with females for alcohol (8.5% vs. 4.4%) and illicit drugs (3.4% vs. 1.9%; SAMHSA, 2015). However, females frequently progress faster from initial use to SUD diagnosis (i.e., “telescoping”; Lewis, Hoffman, & Nixon, 2014; but cf. Keyes, Martins, Blanco, & Hasin, 2010). Females also report greater drug craving (e.g., Kennedy, Epstein, Phillips, & Preston, 2013), and they may be more vulnerable to relapse (Bobzean,

²There are interesting differences in rates of drug use and SUDs across countries and cultures (Gowing et al., 2015) that depend on drug availability, social approval, and other environmental factors, which are outside of the scope of this chapter (e.g., compare the rates of alcohol drinking and alcohol use disorders among the United States, Czech Republic, and Saudi Arabia).

DeNobrega, & Perrotti, 2014). These differences highlight the need to consider sex or gender in all future SUD research (including effects of menstrual phase; Hallam, Boswell, DeVito, & Kober, 2016).

Trends among racial and ethnic groups have also been observed (SAMHSA, 2015). In U.S. adults, past-year SUDs for drugs and alcohol (excluding tobacco) are most prevalent among Native Americans (17.5%), followed by African Americans (9.1%), Whites (8.3%), and Asians (4.7%). Past-year cigarette use is also most prevalent among Native Americans (40.3%), followed by African Americans (28.2%), Whites (27.6%), and Asians (13.4%). These trends are especially important to mention in light of the large gap in rates of drug-related incarceration. Specifically, the U.S. Department of Justice reports that 31.7% of those arrested for drug-related violations are African American (Snyder, 2012), even though African Americans compose at most 16.3% of illicit drug users and 22.1% of those with SUDs involving illicit drugs. Indeed, Whites still account for most cases of SUDs, numerically (approximately 13 million per year, not including nicotine; for further discussion on racial disparities, see Mauer, 2011).

Socioeconomic status (SES) may also be associated with drug use and SUDs. Low SES in childhood is prospectively associated with increased risk of initiation of cigarette smoking and transition to regular use (Gilman, Abrams, & Buka, 2003). In adulthood, low SES is associated with heavier smoking, and lower levels of education are associated with greater severity of tobacco or nicotine use disorders and lower intentions to quit (Siahpush, McNeill, Borland, & Fong, 2006). Lower SES is also linked to higher rates of alcohol use disorders (Poulton et al., 2002), alcohol-related problems (Grittner, Kuntsche, Graham, & Bloomfield, 2012), and SUDs more generally (Compton, Thomas, Stinson, & Grant, 2007). However, SES may not reliably predict subsequent development of SUDs (Bijl, Ravelli, & van Zessen, 1998) and SES during childhood is not a significant predictor of SUD outcome (Tarter et al., 2003).

Finally, SUDs are particularly prevalent in individuals with other (comorbid) psychiatric diagnoses. A history of psychiatric disorders in adolescence increases the risk of using drugs or alcohol and the

transition from casual drug use to SUDs (Conway, Swendsen, Husky, He, & Merikangas, 2016). Cross-sectionally, 36.8% of individuals with one or more SUDs in 2014 had a co-occurring psychiatric disorder (SAMHSA, 2015), including mood, anxiety, personality, and posttraumatic stress disorders, in both adults (Compton et al., 2007) and adolescents (Conway et al., 2016). Similarly, those diagnosed with a psychiatric disorder are at least twice as likely to also suffer from an SUD (Conway, Compton, Stinson, & Grant, 2006). For instance, the association between schizophrenia and tobacco–nicotine use disorder may be particularly strong: Of those with schizophrenia, 60% to 90% smoke cigarettes regularly (D'Souza & Markou, 2012).

RISK FACTORS

As far as we know, anyone who uses drugs may eventually develop an SUD, including (ironically) health care professionals who specialize in addiction treatment (Baldisseri, 2007). However, several factors appear to make some individuals more susceptible to developing SUDs, including genetic, personality, and environmental risk factors. Recent research on genetic factors has documented heritability in general SUD risk, which may represent broad genetic liability for externalizing disorders (along with personality traits related to poor impulse control and sensation seeking; Kendler et al., 2012). Moreover, twin studies have found that 35% to 75% of the variance in SUDs for specific drugs can be attributed to heritable influences, including hallucinogens, stimulants, cannabis, sedatives, cigarettes, alcohol, cocaine, and opiates (for reviews, see Agrawal & Lynskey, 2008; Bevilacqua & Goldman, 2009). However, the search for particular genetic variants that contribute to genetic risk—for specific SUDs or across SUDs—is still ongoing. Many candidate genes have been proposed, some of which appear to affect specific SUDs, whereas others appear to increase risk across SUDs (Bierut, 2011). Interestingly, at least one genetic variant (*CHRNA5*) appears to increase risk for tobacco–nicotine use disorder but protect against cocaine use disorder (Grucza et al., 2008), illustrating the unexpected ways in which genes may

interact with SUD vulnerability. Ultimately, specific genetic markers remain elusive, likely because of the complex polygenic nature of SUDs (Hall, Drgonova, Jain, & Uhl, 2013).

Certain personality traits may also contribute to SUD vulnerability. One such factor is self-control, and the related capacity to regulate emotions, which predicts drug use and SUDs, even when measured as early as preschool (for a recent review, see Kober, 2014). For example, in the now-classic marshmallow test, children are presented with the option of receiving an immediate small reward (a marshmallow) or waiting for a larger reward (e.g., two cookies; Mischel et al., 2011). Studies have shown that the ability to delay gratification and wait for the larger reward is related to several life outcomes in adulthood, including lower likelihood of using crack cocaine, particularly in individuals sensitive to social rejection (Ayduk et al., 2000). In another large study, 1,000 children were assessed on various self-control measures including emotion regulation. Strikingly, those who scored lowest on measured self-control were more than 3 times as likely to report polysubstance SUD in adulthood (Moffitt et al., 2011). The conceptually related construct of impulsivity—the tendency to act without thought or regard for consequences—has also been associated with drug use, SUD vulnerability, severity, and treatment outcomes (for reviews, see de Wit, 2009; Ivanov, Newcorn, Morton, & Tricamo, 2011; Loree, Lundahl, & Ledgerwood, 2015). Importantly, both self-regulation and impulsivity are related to externalizing traits and conduct disorder, which also increase risk for SUDs (Brennan, Hyde, & Baskin-Sommers, 2017), as do comorbid psychiatric diagnoses (Conway et al., 2016).

Critically, early onset of drug use is an important risk factor for the development of SUDs. Adolescent onset of any drug use is associated with subsequent use of additional drugs (Kandel, 1975), rates of SUDs (Chen, Storr, & Anthony, 2009; Wittchen et al., 2008), and SUD severity (Hingson, Heeren, & Winter, 2006), even when genetic and environmental factors are taken into account (Lynskey et al., 2003). Adolescent sensitivity and vulnerability to drug use is attributable, in part, to incomplete development of the prefrontal cortex (PFC), a brain

region associated with executive functioning and top-down cognitive control (Casey, Jones, & Hare, 2008). PFC underdevelopment may also account for adolescents' increased vulnerability to harmful drug effects; indeed, greater cognitive deficits have been reported with earlier onset of alcohol (Zeigler et al., 2005) and marijuana use (Meier et al., 2012; Pope et al., 2003).

Environmental and social factors are also important risk factors for early use, as well as SUDs. For example, longitudinal studies have suggested that the presence of drug-using peers predicts drug use initiation, including for alcohol (Trucco, Colder, & Wiczorek, 2011), cigarettes (Urberg, Değirmencioglu, & Pilgrim, 1997), and marijuana (Kosterman, Hawkins, Guo, Catalano, & Abbott, 2000). Similarly, low teacher or peer support and gang affiliation are associated with early drug use (Katz, Webb, & Decker, 2005; Samdal, Wold, Klepf, & Kannas, 2000). Furthermore, positive attitudes about drug use among family members or peers also increase risk of drug use (e.g., Ary, Tildesley, Hops, & Andrews, 1993). Relatedly, family history is a potent risk factor for drug use and many SUDs, such that having a first-degree relative with an SUD increases the risk by eightfold (Merikangas et al., 1998). Finally, as reported earlier, low SES is also a risk factor for the development of SUDs (Compton et al., 2007).

Stress is another environmental factor that increases vulnerability to SUDs (Sinha, 2008). In fact, overwhelming evidence has demonstrated an association between drug use and different types of stress, including childhood trauma or maltreatment (Hamburger, Leeb, & Swahn, 2008; Heffernan et al., 2000), posttraumatic stress disorder (Flanagan, Korte, Killeen, & Back, 2016), lifetime exposure to stressors (Turner & Lloyd, 2003), and recent negative life events (Newcomb & Harlow, 1986). In particular, stress during childhood has been associated with increased risk of developing SUDs later in adulthood (Andersen & Teicher, 2009; Nelson et al., 2006). In one cohort of 8,613 adults, experiencing five or more childhood adversities (e.g., parental abuse, neglect, familial dysfunction) was associated with a seven- to 10-fold increase in the likelihood of SUDs (Dube et al., 2003). Moreover, stress is associated with increased risk of relapse (Koob & Kreek, 2007;

Sinha, 2001) and poor treatment outcomes (e.g., Krueger, 1981), possibly because of its amplifying effect on craving (Sinha, Shaham, & Heilig, 2011). Relatedly, the tendency to experience negative affect is also related to SUD initiation and maintenance (see Kober, 2014, for review).

NEUROBIOLOGY OF SUBSTANCE USE DISORDERS

Over the past few decades, research has begun to uncover the neural processes involved in drug taking and the transition into SUDs. One critical early finding showed that all addictive drugs used by humans are associated with increased dopamine (DA) in the ventral striatum and nucleus accumbens (Di Chiara & Imperato, 1988). Indeed, although each drug has a distinct primary mechanism of action (Pierce & Kumaresan, 2006), they also converge on a common secondary mechanism in the mesolimbic DA pathway and its dopaminergic projections from the ventral tegmental area to the ventral striatum and nucleus accumbens (Di Chiara & Imperato, 1988; Nestler, 2005). This pathway has long been associated with the concept of reward and has since been specifically implicated in the reinforcing effects of addictive drugs (Wise, 2004). Furthermore, drug-evoked plasticity in this circuit has been linked directly to compulsive drug taking and to the development of cue-induced craving and drug seeking (for a recent review, see Lüscher, 2016). Although many of the insights in this field have been gleaned from animal research, human studies using positron emission tomography have also linked drug administration with increased DA in the striatum (including the ventral striatum; for a review, see Volkow, Wang, Fowler, Tomasi, & Telang, 2011). More important, the acute activation of the DA system is not unique to drugs but is also observed with other rewards, including food (Martel & Fantino, 1996) and sexual behavior (Balfour, Yu, & Coolen, 2004), which suggests that drugs usurp a system that evolved to mediate these natural rewards (Koob & Le Moal, 2001; Volkow, Fowler, Wang, & Swanson, 2004).

In parallel, Schultz, Dayan, and Montague (1997) showed that DA neurons fire in response

to unexpected rewards and to reward-predicting cues, suggesting a role for DA in reward learning and reward prediction error. Taken together, these findings serve as the basis for a dopamine theory of addiction (e.g., Lüscher, 2016; Volkow & Morales, 2015; Wise, 2004). Although this DA theory has been challenged (e.g., Nutt, Lingford-Hughes, Erritzoe, & Stokes, 2015), with evidence of DA-independent reinforcement for some drugs (Pierce & Kumaresan, 2006), the DA circuit continues to serve as the basis of most neurobiological models of SUDs. For example, compulsive drug taking has been explained in terms of DA-mediated incentive sensitization (rather than reward value), such that drugs are assigned higher incentive salience, resulting in increased drug wanting or craving (Robinson & Berridge, 2003). In this view, mesolimbic DA is associated with enhanced motivation to take drugs but not with increased pleasure from drug use (Berridge & Kringelbach, 2015). This is consistent with preliminary findings that drug-induced increases in DA in the ventral striatum correlate not with liking for the drug, but with drug craving (Evans et al., 2006; Leyton et al., 2002; Smith, Dang, Cowan, Kessler, & Zald, 2016; but cf. Pool, Sennwald, Delplanque, Brosch, & Sander, 2016). Other learning-based models emphasize the transition from goal-directed behavior and DA signaling in ventral striatum to conditioned stimulus–response associations in a “habit circuit” involving DA in the dorsal striatum (Belin, Belin-Rauscent, Murray, & Everitt, 2013; Everitt & Robbins, 2016). Other formulations implicate alterations in the hypothalamic–pituitary–adrenal axis (Koob, 2008) or insular circuitry related to interoception and self-awareness (Moeller & Goldstein, 2014; Naqvi & Bechara, 2010; Paulus & Stewart, 2014).

Finally, many neurobiological accounts of addiction implicate executive control circuitry, including subregions of the PFC (e.g., Everitt & Robbins, 2016; Feil et al., 2010; Goldstein & Volkow, 2011; Koob & Le Moal, 2001; Volkow & Baler, 2015; Volkow et al., 2011). Accordingly, compulsive drug taking is attributed to cognitive control deficits and underlying PFC dysfunction resulting in impaired decision making and reduced inhibition (including reduced regulation of craving). In turn, this is consistent with the view

of SUD as a disorder of self-regulation (Goldstein & Volkow, 2002; Heatherton & Wagner, 2011). Consistently, many studies have reported impaired cognitive control abilities in SUDs, along with disruptions in PFC structure and function (e.g., Goldstein & Volkow, 2011; Kober, DeVito, DeLeone, Carroll, & Potenza, 2014). Such PFC disruptions are particularly important because PFC recruitment underlies the capacity to regulate craving (Kober, Mende-Siedlecki, et al., 2010; Volkow et al., 2010; and see below), and successful abstinence relates to improvements in PFC function (Garavan, Brennan, Hester, & Whelan, 2013). Ultimately, the various neurobiological accounts reviewed in this section are not mutually exclusive, and it is generally acknowledged that alterations in reward, habit, salience–attribution, and executive control systems are all required to explain addictive behaviors and the transition to SUDs (Volkow et al., 2011).

THEORETICAL AND PSYCHOLOGICAL MODELS

SUDs are complex conditions that can manifest in diverse ways depending on the drug involved, pattern of use, stage of addiction, symptoms endorsed, and other intrinsic and extrinsic factors. Thus far, many theoretical models have been proposed to explain SUDs, each focusing on different but characteristic aspects of the disorder. Here, we briefly introduce just a few of them, although none fully captures the many facets of SUDs (for additional reviews, see Bahr & Hoffmann, 2016; Teesson, Hall, Proudfoot, & Degenhardt, 2013).

Two philosophical approaches—the moral and disease models—address the question of who is responsible for the development of and recovery from SUDs. The moral model attributes SUDs to “moral or character defects” (Wilbanks, 1989, p. 408). In this view, SUDs are a result of poor choices made by individuals who lack willpower or moral strength. Thus, addicted individuals are personally responsible for developing the problem, and the appropriate treatment is punishment (Wilbanks, 1989). This view remains prevalent in society today, as is evident in the ongoing criminalization of drug use, the “Just Say No” campaign, and the extant public stigmatizations of drug use

(Parcesepe & Cabassa, 2013), even among health professionals (van Boekel, Brouwers, van Weeghel, & Garretsen, 2013). Unfortunately, such negative attitudes represent major barriers to treatment admission, efficacy, and recovery (CASA Columbia, 2012; van Boekel et al., 2013).

More recently, identification of biological and genetic factors that contribute to SUDs (as reviewed above) gave rise to the disease model that regards SUDs as medical conditions that require treatment and care (Leshner, 1997; Wise, 2000). According to this model, drug taking is initially voluntary, but over time, long-lasting neuroadaptations render drug-taking behavior compulsive and potentially uncontrollable. This model is especially supported by evidence of significant heritability for SUDs (Agrawal & Lynskey, 2008; Bevilacqua & Goldman, 2009) as well as findings that link drug taking with disruptions in neural substrates associated with reward and inhibitory control (for review, see Baler & Volkow, 2006; Lüscher, 2016). As such, this model views SUDs as a pathophysiological problem rather than an ethical one. However, although the disease model rests on some scientific evidence, it remains open for debate. First, unlike other chronic diseases, SUDs have to be actively maintained via continuous drug taking. Furthermore, the disease model does not account for “natural” recovery without the use of professional help, which is rare in other chronic diseases but is observed in some SUDs (Sobell, Cunningham, & Sobell, 1996; Waldorf, 1983). In addition, the disease model cannot account for findings of reduced drug preference in the presence of alternative reinforcers (Higgins, Bickel, & Hughes, 1994; Kirkpatrick et al., 2012; Petry, Martin, Cooney, & Kranzler, 2000). Thus, the extent to which an addicted individual can control drug taking remains to be determined (e.g., Carroll et al., 2014; Lopez, Onyemekwu, Hart, Ochsner, & Kober, 2015).

Other psychological models directly describe the motivation underlying drug use, considering it a disorder of self-regulation (for review, see Kober, 2014). For example, the self-medication model hypothesizes that individuals initiate and maintain drug use to relieve painful affect or to control their emotions, formulating SUDs as disorders of

self-regulation (Khantzian, 1985, 2015). In this view, individuals self-select drugs to fulfill their specific emotional needs. Although this model has been challenged, several lines of evidence have supported it (for review, see Kober, 2014). For example, individuals with chronic pain are far more likely to develop SUDs for pain-reducing drugs such as opiates than healthy, pain-free adults (Morasco et al., 2011). This model relates to broader psychodynamic models that posit that drugs are taken as a form of self-regulation or defense against intrapsychic conflict (Dodes, 2009; Morgenstern & Leeds, 1993). However, there is much less empirical research testing these models, possibly because of the difficulty of quantitatively assessing psychodynamic variables (Shedler, 2010).

Reinforcement models provide a behavioral framework to understand how drug use is initiated and maintained (Wise & Koob, 2014). Historically, they have relied on the consistent observation that animals will readily self-administer all of the addictive drugs used by humans (Deneau, Yanagita, & Seevers, 1969) and will work to obtain them (Pickens & Harris, 1968), suggesting that drugs are reinforcing across species (Schuster & Thompson, 1969; Stolerman, 1992). Subsequently, such models differentiate between positive and negative reinforcement, positing that each reinforcement type is associated with a different stage in the development and maintenance of SUDs. First, drugs lead to increases in dopamine (Wise, 1998) that exceed levels achieved by natural rewards (Di Chiara & Imperato, 1988). This is thought to create euphoric drug effects and provide positive reinforcement, which accounts for the initial transition from experimental drug use to repeated use (Koob et al., 2004). On continued use, drug tolerance develops and any cessation of use is characterized by withdrawal. In this stage, drug use is negatively reinforced via alleviation of aversive withdrawal effects, which further contributes to the development and maintenance of SUDs (Wise & Koob, 2014). At the other end of the spectrum are social learning models (e.g., Akers, Krohn, Lanza-Kaduce, & Radosevich, 1979), which posit that learning occurs in social contexts, in the absence of direct reinforcement, provoked initially by observation and imitation of parents, peers, or popular media. In addition,

transition into regular drug use may be facilitated through positive social feedback. However, little data exist to validate these models.

Perhaps the broadest view is the multilevel approach embodied in diathesis–stress models (Windle, 2010). Such models describe the conjoint influence of variables from multiple levels of analysis on the development of SUDs, including genetic factors, personality dispositions, and life stressors (Windle, 2010). This approach is therefore supported by many of the findings reviewed earlier, including genetic heritability of SUDs, contribution of personality factors to SUD risk, and the association between SUDs and life stress. Furthermore, research has identified direct interactive effects between several genes and stressful experiences that together influence drug use and addiction outcomes (for review, see Enoch, 2011). Gene–environment interactions may also contribute to SUD through their effects on comorbid depression (Ressler et al., 2010) and personality traits (Enoch, Steer, Newman, Gibson, & Goldman, 2010) that have been linked to drug use and SUDs (Elkins, McGue, & Iacono, 2007; Niemelä et al., 2006).

ROLE OF CRAVING IN SUBSTANCE USE DISORDERS

Although craving just recently became a diagnostic criterion (defined as “a strong desire”; American Psychiatric Association, 2013), it has long been considered a core feature of SUDs (Goldstein & Volkow, 2002; O’Brien, Childress, Ehrman, & Robbins, 1998; Volkow et al., 2006; Wikler, 1948; Wise, 1988). Several lines of evidence have consistently linked drug craving to drug use and relapse (for a detailed review, see Kober & Mell, 2015). In retrospective studies, craving is often cited as a reason for relapse by cigarette smokers (Nørregaard, Tønnesen, & Petersen, 1993; Peterson, Lonergan, Hardinge, & Teel, 1968), alcohol drinkers (Maisto, O’Farrell, Connors, McKay, & Pelcovits, 1988), and heroin users (Heather, Stallard, & Tebbutt, 1991). Prospective studies have shown that craving predicts subsequent drug use and relapse for cigarettes (Herd, Borland, & Hyland, 2009; Killen & Fortmann, 1997), alcohol (Bottlender & Soyka, 2004;

Law et al., 2016), marijuana (Cousijn, van Benthem, van der Schee, & Spijkerman, 2015), cocaine (Weiss et al., 2003), methamphetamine (Hartz, Frederick-Osborne, & Galloway, 2001), and opioids (Tsui, Anderson, Strong, & Stein, 2014). Furthermore, studies that use ecological momentary assessment procedures have linked temporal variations of craving in real-life situations to subsequent drug use. Ecological momentary assessment involves prompting participants to provide electronic reports of craving and drug taking in everyday life. These studies have demonstrated that craving not only increases before drug taking (Preston et al., 2009) but also predicts drug taking (T. M. Moore et al., 2014; Serre, Fatseas, Swendsen, & Auriacombe, 2015; Shiffman et al., 1997).

Several researchers have begun to differentiate tonic craving—that varies naturally and is associated with withdrawal—from cue-induced craving—which is a form of cue reactivity and is reliably evoked by various drug-related stimuli (e.g., paraphernalia; B. L. Carter & Tiffany, 1999). A growing body of work has suggested that cue-induced craving also contributes to drug use and relapse. First, the presence of drugs or drug-associated cues has been linked to drug use in retrospective (Gawin & Kleber, 1986; Shiffman, 1982) and ecological momentary assessment studies (Epstein et al., 2009; Shiffman et al., 2002). In addition, prospective studies have shown that laboratory cue-induced craving predicts drug use and relapse after treatment for cigarettes (e.g., Powell, Dawkins, West, Powell, & Pickering, 2010), alcohol (e.g., Litt, Cooney, & Morse, 2000), and heroin (e.g., Fatseas et al., 2011). Furthermore, studies assessing the effects of cues on *in vivo* cigarette smoking have shown that cue exposure increased both craving and smoking (Hogarth, Dickinson, & Duka, 2010; Shiffman et al., 2013). Taken together, this evidence suggests that craving is a powerful predictor of drug use and relapse. A recent meta-analysis quantified the influence of both tonic and cue-induced craving on subsequent laboratory measures of smoking with a small to medium effect size, accounting for as much as 11.5% of the variance in smoking behavior (Gass, Motschman, & Tiffany, 2014). Additional meta-analyses are needed to evaluate the magnitude of effects in treatment settings and across drug types.

Given the critical role of craving in drug use, several empirically validated treatments for SUDs focus on teaching strategies for regulation of craving (see Treatment section below), and those who learn such strategies during treatment demonstrate better long-term outcomes (e.g., Kiluk, Nich, Babuscio, & Carroll, 2010). Ecological momentary assessment studies have also suggested that the use of cognitive strategies during craving is associated with reduced craving and reduced relapse (e.g., O'Connell, Hosein, Schwartz, & Leibowitz, 2007). Investigating the neural correlates of craving and cue reactivity, several meta-analyses revealed consistent activation in regions including the ventral striatum and amygdala during exposure to drug-related cues (e.g., Chase, Eickhoff, Laird, & Hogarth, 2011; Kühn & Gallinat, 2011), which is consistent with neurobiological accounts of SUDs. In addition, activation in these regions correlates positively with self-reported craving, suggesting that they may be part of a circuit that underlies both cue reactivity and the conscious experience of craving (for discussion of insula, see Garavan, 2010; Naqvi, Gaznick, Tranel, & Bechara, 2014). Furthermore, several studies have linked neural cue reactivity to subsequent drug use (Grüsser et al., 2004; Kosten et al., 2006; Li et al., 2015; Seo et al., 2013). Thus, the neural signature of cue reactivity may join tonic and cue-induced craving as treatment targets and predictors of treatment outcome.

TREATMENT

Despite decades of research, there is no cure for SUDs. Indeed, even gold-standard treatments are only moderately effective at reducing drug use, and the modal outcome is relapse (Dutra et al., 2008; Feldstein Ewing & Chung, 2013). Even worse, the majority of those with an SUD remain outside of the treatment system. Only 12.1% of individuals with an SUD (except tobacco) receive treatment at a specialized facility every year (i.e., hospitals, mental health centers; SAMHSA, 2015).

Many aspects of SUDs complicate treatment as well as treatment assessment, including the varied nature of the disorder. Indeed, each patient's presentation depends on the drugs used, symptom

clustering, life circumstances, and other factors, resulting in a wide spectrum of individual needs. These needs may or may not match with available treatment modalities at any point in time, and this may or may not matter for treatment efficacy (Project MATCH Research Group, 1998). Moreover, common polysubstance use and comorbidity with other psychiatric disorders may increase resistance to treatment and reduce treatment efficacy (e.g., Arndt, McLellan, Dorozynsky, Woody, & O'Brien, 1994; Hasin et al., 2002), and there may be gender-specific effects (Hallam et al., 2016). In addition, because the causes of SUDs have yet to be fully elucidated, treatments do not, and cannot, target any underlying mechanisms. Instead, treatments attempt to reduce drug-related harm and drug use itself. Assessment of drug use outcomes is further complicated by the fact that SUDs are chronic conditions, and abstinence is often punctuated by lapses and relapses (Dutra et al., 2008). Thus, there is an urgent need to identify and clarify core processes that underlie SUDs, as well as those that underlie treatment-related change, to improve on the current approaches.

The three commonly defined stages of SUD treatment are detoxification, recovery, and relapse prevention (Potenza, Sofuoglu, Carroll, & Rounsaville, 2011). Although controlled drug use may be a reasonable treatment goal (Saladin & Santa Ana, 2004), the common goal of the detoxification stage is to safely terminate drug use, reduce withdrawal symptoms, and achieve complete abstinence. The onset, duration, and methods used in this stage depend on the specific drug and treatment type. Detoxification is often, but not necessarily, the first stage of treatment because it may also be initiated on a formal quit date during the recovery stage. In the recovery stage, individuals develop the motivation and skills to maintain abstinence (e.g., strategies to regulate emotion and craving; Potenza et al., 2011). The final stage is relapse prevention, which focuses on developing strategies to sustain long-term abstinence and adopting a drug-free lifestyle. Unfortunately, because relapse is common (Dutra et al., 2008), many individuals revisit each stage multiple times within cycles of relapse, treatment reentry, and recovery (Scott, Dennis, & Foss, 2005).

Treatments can be further divided into pharmacological (medication) and psychosocial treatments, which can be administered in combination. The few medications currently approved by the U.S. Food and Drug Administration can be further divided into two groups: (a) agonists, which work by mimicking the neural action of the drug (and are more common), and (b) antagonists, which have the opposite action (e.g., naltrexone for opioids and alcohol). Agonist medications are specific to each addictive drug as a form of substitution therapy, allowing safe and gradual detoxification. Such agonists include methadone and buprenorphine for heroin, benzodiazepines for alcohol, and nicotine replacements (e.g., gum) or varenicline for cigarettes. Substitution medications aim to lower the risk of relapse by reducing withdrawal symptoms, craving, and euphoria if the drug is taken (Veilleux, Colvin, Anderson, York, & Heinz, 2010) and to reduce drug-related adverse health effects (i.e., the toxins contained in cigarette smoke). Several meta-analyses have validated the efficacy and safety of agonists in reducing drug use and withdrawal, including nicotine replacement for cigarettes (D. Moore et al., 2009), benzodiazepines for alcohol (Holbrook, Crowther, Lotter, Cheng, & King, 1999), and methadone and buprenorphine for heroin (Farré, Mas, Torrens, Moreno, & Camí, 2002; Meader, 2010). Consistently, 78.5% of all detoxifications across the United States are medication assisted (SAMHSA, 2014); this is especially important for alcohol detoxification because acute withdrawal can be fatal (Mayo-Smith et al., 2004). There are no medications approved for treatment of stimulant use.

Psychosocial (nonpharmacological) treatments are used at the recovery and maintenance stages and aim to modify drug-related attitudes and behaviors to achieve long-term abstinence. One such attitude (which is especially important for treatment initiation) is motivation for change, which is at the basis of motivational enhancement therapy or motivational interviewing (MI; Miller & Rollnick, 2002). MI is often described as a conversational or counseling style that may help individuals resolve their ambivalence and strengthen their readiness to change (Magill et al., 2014; Rollnick & Allison, 2004). Clinically, MI uses both relational and

technical elements including empathic listening, collaborative conversation, and complex reflections to reduce resistance and increase the patient's "change talk." In turn, this is hypothesized to mediate treatment efficacy (Magill et al., 2014). A recent study showed that neural activity during change talk consistently correlated with reductions in cannabis use after MI (Feldstein Ewing et al., 2013). Overall, several meta-analyses established small but significant effects of MI on alcohol use (Vasilaki, Hosier, & Cox, 2006), cigarette use (Hettinger & Hendricks, 2010), and adolescent drug use (Jensen et al., 2011). Other studies have shown that MI reduces use of other drugs (e.g., marijuana and cocaine; Martino, Carroll, Nich, & Rounsaville, 2006; Satre et al., 2016). However, MI may be most effective as an adjunct or prelude to other therapies by increasing initiation of or engagement with treatment (Burke, Dunn, Atkins, & Phelps, 2004).

Cognitive behavioral therapy (CBT) was originally developed for depression (Beck, 2011) and is perhaps the most studied psychotherapy across different forms of psychopathology (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012). CBT has been adapted for SUDs (Carroll, 1998; Kadden, 1995) and has since been validated across multiple randomized controlled trials (e.g., Carroll et al., 2004) and meta-analyses, revealing small to medium effect sizes (Dutra et al., 2008; Irvin, Bowers, Dunn, & Wang, 1999; Magill & Ray, 2009). Broadly, CBT for SUDs uses functional analysis to help individuals recognize high-risk situations in which they are most likely to crave, seek, and use drugs. In addition, it includes skills training such as situation avoidance, regulation of negative emotion, regulation of craving, and decision making to help individuals reduce drug taking. More recently, a computerized version of CBT was also shown to reduce drug use (Carroll et al., 2008, 2014). Computerized treatments have several advantages in allowing broad distribution at low cost, access at any time of day, reduced stigma with increased confidentiality, and standardized delivery (Carroll & Rounsaville, 2010). As such, they hold great potential for reaching the vast pool of individuals with SUDs who currently cannot or do not access treatment (Carroll, 2014). However, computerized

treatments are relatively new and require more rigorous evaluation of their therapeutic effects across SUD populations before they are widely disseminated (Cunningham & Van Mierlo, 2009).

The mechanisms underlying the efficacy of CBT are an area of active investigation (Feldstein Ewing et al., 2013). It has long been suggested that acquisition of coping skills during CBT may be one such underlying mechanism (Kober, 2014; Potenza et al., 2011). Indeed, skills increase from pre- to post-CBT, and individuals who acquired more skills in CBT have higher rates of abstinence during and after treatment (Carroll, Nich, Frankforter, & Bisighini, 1999). Furthermore, the quality of acquired coping skills were shown to mediate the effect of CBT on abstinence (Kiluk et al., 2010). One hypothesis is that this increase in skills depends on improvement in PFC function after CBT (Potenza et al., 2011). Consistently, we (and others) have shown that CBT strategies are effective in regulating craving (Kober, Kross, Mischel, Hart, & Ochsner, 2010) and reducing smoking (Kober, Lopez, & Ochsner, 2017), and they depend on recruitment of PFC (i.e., greater recruitment is associated with reduced craving; Giuliani, Calcott, & Berkman, 2013; Kober, Mende-Siedlecki, et al., 2010; Volkow et al., 2010). In another recent study, we showed increased PFC efficiency from pre- to post-CBT treatment (DeVito et al., 2012), which is consistent with improvement in emotion regulation and cognitive control (Buhle et al., 2014). Although these data are promising, their interpretation is complicated by the fact that CBT treatment engagement requires a minimal degree of cognitive functioning, and SUDs are frequently accompanied by cognitive deficits as well as altered structure and function of PFC circuits (Goldstein & Volkow, 2011). Indeed, pretreatment cognitive deficits predict low treatment retention and worse outcomes (Aharonovich et al., 2006; Bates, Pawlak, Tonigan, & Buckman, 2006), possibly because of lack of attention or comprehension. Thus, it may be important to consider baseline cognitive functioning in research and in the clinic.

Contingency management (CM) is a reinforcement-based intervention that applies the principles of operant conditioning to drug use by rewarding abstinence with money or prizes (Petry et al.,

2000). CM was shown to increase treatment retention (Petry et al., 2000) and medication compliance (Preston et al., 1999), and meta-analyses have established its efficacy in reducing drug use (Benishek et al., 2014; Prendergast, Podus, Finney, Greenwell, & Roll, 2006). However, the effects of CM may be short lived: Although a few studies have observed long-term reductions in drug use (Petry & Martin, 2002; Rawson et al., 2006), the most recent meta-analysis indicated no significant effect of CM 6 months after treatment (Benishek et al., 2014). Thus, CM (like MI) may be most effective in conjunction with other treatment approaches. Indeed, adding a CM component to other treatments (e.g., CBT) reduces cigarette smoking (Morean et al., 2015) and methamphetamine use (Roll et al., 2006). Similarly, a recent trial observed the additive effect of CM and CBT on cocaine use, with effects sustained at 1-year follow-up (Carroll et al., 2016). Thus, although the use of CM is not currently prevalent in clinical practice, these data suggest that it can contribute to abstinence, at least in the short term.

In the past decade, there has been growing interest in mindfulness-based therapies (MBTs) for SUDs. Mindfulness is originally a Buddhist concept; in modern psychology, it is often defined as a two-component construct: self-regulation of attention to the present moment coupled with an attitude of acceptance and curiosity toward the present moment (Bishop et al., 2004). Mindfulness is often practiced through mindfulness meditation, which consists of focusing attention on one's immediate internal experience (e.g., sensations, breathing, thoughts, emotion), and regarding it nonjudgmentally, with acceptance. In turn, this cultivates the ability to observe one's own experience without getting caught up in it, which facilitates skillful responding (rather than automatic reaction; e.g., Witkiewitz et al., 2014; Zgierska et al., 2009). One of the earliest MBTs for SUDs is mindfulness-based relapse prevention (Bowen, Chawla, & Marlatt, 2011), which incorporates mindfulness meditation and skills into CBT, to specifically target drug craving and negative affect that increase drug use. Although research in this area is relatively new, a recent meta-analysis concluded that MBTs are effective for alcohol, cocaine, amphetamines, marijuana,

cigarettes, and opiates (Chiesa & Serretti, 2014). Several studies have specifically shown that MBTs may be particularly effective at longer follow-up (Bowen et al., 2014; Brewer et al., 2011; Davis, Manley, Goldberg, Smith, & Jorenby, 2014; Vidrine et al., 2016).

One mechanism by which MBTs decrease drug use may be the reduction of craving (Bowen et al., 2009; Davis et al., 2014; Elwafi, Witkiewitz, Mallik, Thornhill, & Brewer, 2013; Witkiewitz & Bowen, 2010) and negative affect (Witkiewitz & Bowen, 2010; Witkiewitz, Lustyk, & Bowen, 2013). We have consistently shown that mindfulness is an effective strategy to reduce craving and craving-related neural activity in cigarette smokers (Westbrook et al., 2013). In another study, we showed that individuals who underwent mindfulness training smoked less and also exhibited reduced stress-related neural activity; an important finding is that these reductions related to better treatment outcomes (Kober, Brewer, Tuit, & Sinha, 2017). Interestingly, in both studies, we did not observe increased PFC recruitment, as is observed in cognitive regulation of craving and negative emotion (Buhle et al., 2014; Kober, Mende-Siedlecki, et al., 2010; Volkow et al., 2010), suggesting that mindfulness reduces emotional reactivity via a bottom-up process (Witkiewitz et al., 2013). These results have significant clinical implications, in particular for SUD patients who may have cognitive impairments (Kober & Mell, 2015).

Finally, 12-step programs may be the most common form of treatment, but their efficacy has not yet been fully established (Ferri, Amato, & Davoli, 2006; Galanter, Dermatis, Stanievich, & Santucci, 2013). Several other approaches have been preliminarily explored, including physical exercise and psychodynamic psychotherapy (e.g., Brown et al., 2010; Leichsenring, 2005), but further systematic research is needed before their efficacy can be determined.

CONCLUSION AND FUTURE DIRECTIONS

SUDs are chronic, relapsing conditions that affect a large proportion of the adult population worldwide, leading to unprecedented social costs. Although they are the most prevalent psychiatric conditions,

they represent only a subset of casual drug users, suggesting that some individuals are more vulnerable to developing SUDs. Known risk factors include a range of genetic, personality, and socioenvironmental factors, as well as their interaction. Notably, several of these factors seem to be domain general (e.g., self-regulation), contributing to SUDs and other disorders. Nevertheless, researchers are still unable to predict the transition to SUD. To this end, large-scale longitudinal studies are needed that begin before the initiation of drug use; incorporate individual differences, behavioral, and imaging measures; and use rigorous prediction models (Whelan & Garavan, 2014).

Several theories have been proposed to explain SUDs and compulsive drug taking. Each theory addresses important aspects of these disorders (e.g., motivation), but none provides a comprehensive explanation; this is in part because of the complex and heterogeneous nature of SUDs. However, evidence is converging on common neurobiological processes involved in SUDs, including long-term alterations in neural systems associated with reward, motivation, and executive control/self-regulation, which underlie the transition from casual to compulsive drug use.

Currently, several pharmacological and psychosocial treatments are available for SUDs, but none are curative. They target drug attitudes, reduction of harm, or abstinence instead of the underlying mechanisms because those have yet to be fully elucidated. Empirically validated psychosocial treatments include MI, CBT, and CM, which are only modestly effective. This underscores an urgent need to improve current treatments and develop new ones. It is possible that a Research Domain Criteria–based approach may improve diagnosis and treatment by encouraging mechanism-focused research at multiple levels of analysis (including sex- or gender-related factors). Computer-based treatments and MBTs are relatively new approaches, and empirical evidence of their efficacy is accumulating. Further research is required to uncover psychological and neural mechanisms underlying these and other effective interventions to improve the ability to treat SUDs (e.g., by including neuroimaging probes in well-controlled, randomized clinical trials). For

example, growing evidence points to the critical role of craving in drug use and relapse, and reductions in craving may be an important mechanism of action across several treatment modalities (e.g., CBT, MBTs). Future studies could investigate this directly by testing the efficacy of regulation-of-craving training as a standalone intervention and by assessing neural changes that may predict abstinence across treatment types. Interestingly, it is unknown whether matching individuals to treatments may improve efficacy (Project MATCH Research Group, 1998). It is our hope that the next decade will bring answers to many of these questions.

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