Substance-Related and Addictive Disorders

14

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Introduction

The Substance-Related and Addictive Disorders section of the Diagnostic and Statistical Manual, 5th edition (DSM-5), encompasses ten substance classes and their disorders and gambling disorder [1]. These diagnostic criteria encompass maladaptive patterns of substance use and gambling behaviors with loss of control, compulsivity, and harmful biological and psychosocial consequences. These are syndromes with common, core symptoms and wide-ranging features depending on the substance, the environment, and the intrinsic characteristics of the individual [2].

Substance-Related Disorders and Gambling Disorder

Introduction

The DSM-5 divides substance-related disorders into substance-use disorders and substance-induced disorders, focusing on ten major substance categories (Fig. 14.1). A substance-use disorder (SUD) is defined as "a problematic pattern of substance use leading to "clinically significant impairment or distress," manifest by at least 2 of 11 criteria over a given year" [1]. Substance-induced disorders consist of substance intoxication, substance withdrawal, and "other substance-induced disorders," which encompass a variety of substance-induced mental disorders covered in other DSM-5 chapters (e.g., opioid-induced anxiety disorders are covered under "Anxiety Disorders"). Note that substance withdrawal is both a substance-induced disorder and a diagnostic criterion for substance-use disorders (see Table 14.3 in the Phenomenology Section).

The nine specific classes (the tenth class is "other") of intoxicating substances identified in the DSM-5 are shown in Fig. 14.1, and the diagnostic conditions are shown in Table 14.1. Of note, while caffeine is recognized as a substance class, the DSM-5 chapter defines caffeine-induced disorders (caffeine intoxication and caffeine withdrawal), but has not yet included caffeine use disorder as an official diagnosis (see section "Future Directions"). Gambling disorder is defined as "persistent and recurrent problematic gambling behavior leading to clinically significant impairment or distress, as indicated by the individual exhibiting at least 2 of 9 criteria in a 12 month period" [1].

Epidemiology of Substance-Related Disorders and Gambling Disorder

According to the 2020 United Nations World Drug Report, on an annual basis, approximately 269 million people globally use intoxicating substances other than alcohol (Fig. 14.2), 35 million people have a substance-use disorder, and 500,000 die because of their substance use [3]. In addition, approximately 38% of the population drinks alcohol, with 3.5–14.8% having an alcohol use disorder, and harmful use resulting in three million deaths and 131 million disability-adjusted life years (DALYs) each year (Fig. 14.3) [4].

The National Survey on Drug Use and Health (NSDUH) provides detailed information about SUD in the United States [5]. As Fig. 14.4 demonstrates, in 2019, among people over the age of 12, over 165 million people (60% of the pop-

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Fig. 14.1 DSM-5 defined substance classes for substance-related disorders

Table 14.1 Substance-related and addictive disorders

Class	Related disorder
Alcohol	Alcohol use disorder
	Alcohol intoxication
	Alcohol withdrawal
Caffeine	Caffeine intoxication
	Caffeine withdrawal
Cannabis	Cannabis use disorder
	Cannabis intoxication (with or without perceptual disturbances)
	Cannabis withdrawal
Hallucinogen	Phencyclidine use disorder
	Other hallucinogen use disorder
	Phencyclidine intoxication
	Other hallucinogen intoxication
	Hallucinogen persisting perception disorder
Inhalant	Inhalant use disorder
	Inhalant intoxication
	Other inhalant-induced disorders

Table 14.1 (continued)

Class	Related disorder
Opioid	Opioid use disorder
	Opioid intoxication (with or without perceptual disturbances)
	Opioid withdrawal
	Other opioid-induced disorders
Sedative, hypnotic, or anxiolytic	Sedative, hypnotic, or anxiolytic use disorder
	Sedative, hypnotic, or anxiolytic intoxication
	Sedative, hypnotic, or anxiolytic withdrawal (with or without perceptual disturbances)
	Other sedative-, hypnotic-, or anxiolytic-induced disorders
Stimulant	Stimulant use disorder E.g., amphetamine-type substance; cocaine
	Stimulant intoxication E.g., amphetamine or other stimulants (with or without perceptual disturbances); cocaine (with or without perceptual disturbances)
	Stimulant withdrawal E.g., amphetamine or other stimulants; cocaine
	Other stimulant-induced disorders
Tobacco-related disorders	Tobacco use disorder
	Tobacco withdrawal
	Other tobacco-induced disorders
Other (or unknown) substance	Other (or unknown) substance-use disorder
	Other (or unknown) substance intoxication
	Other (or unknown) substance withdrawal
	Other (or unknown) substance-induced disorders
	Unspecified other (or unknown) substance-related disorder
Nonsubstance	Gambling disorder

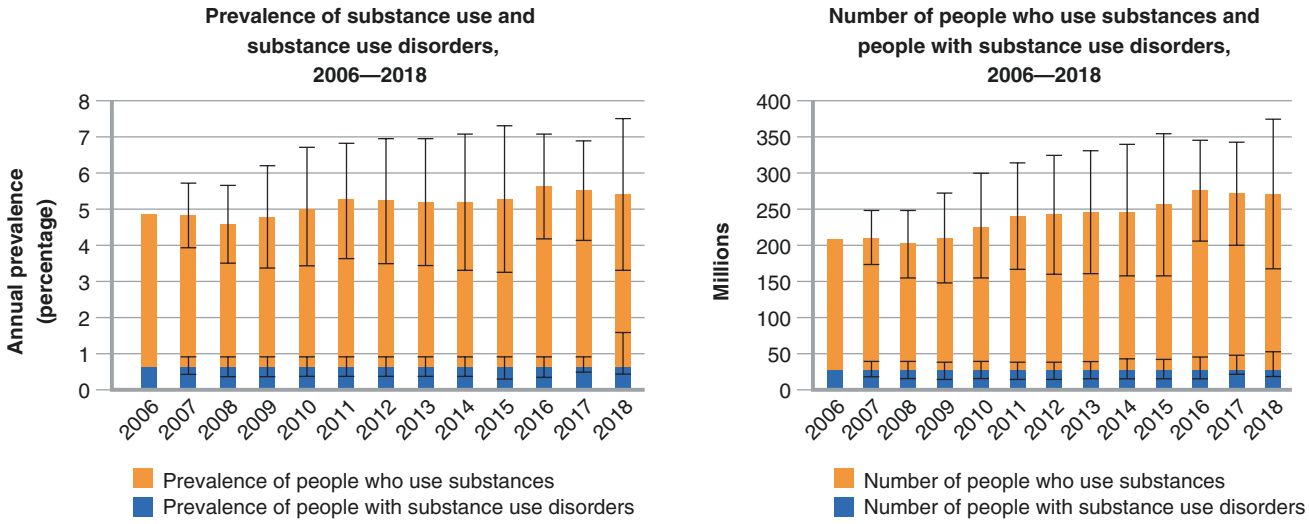


Fig. 14.2 Global prevalence and number of people (in millions) who use substances and have substance-use disorders

ulation) reported using an intoxicating substance in the past month (80% in the past year). Among these, 140 million people used alcohol, 58 million used tobacco, and 31 million used cannabis in the past month. Among illicit drugs, use of prescription opioids was most common, followed by cocaine, sedative-hypnotics, hallucinogens, and stimulants [5].

Additionally, 20 million people (7.4% of the US adult population) had a SUD in the past year. Figure 14.5 shows the breakdown of specific SUDs. The total number is greater than 20 million because over a third of individuals have two or more SUDs. Only 11% of those people actually received treatment at a hospital, a drug or alcohol rehabilitation program, or a mental health center [5].

Figure 14.6 demonstrates how SUD, mental illness, and medical conditions often co-occur as each category of illness can predispose and perpetuate illness in the other categories.

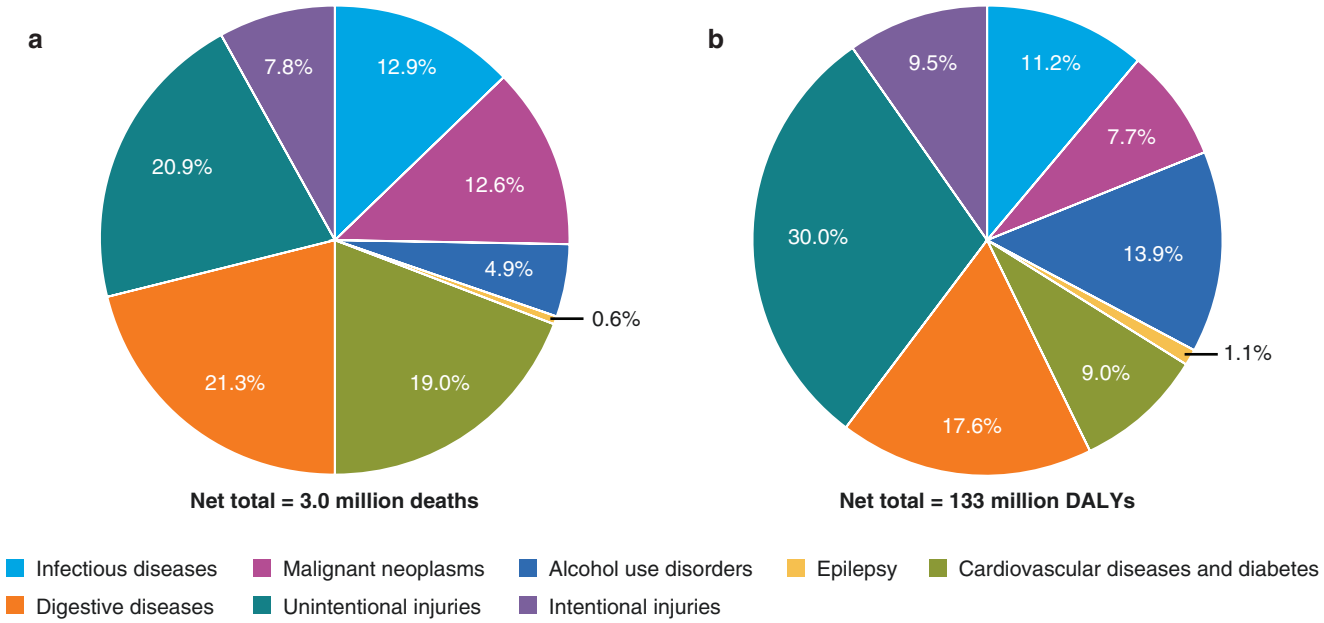


Fig. 14.3 (**a**) Percentage of alcohol-attributable deaths and (**b**) percentage of alcohol-attributable disability-adjusted-life years (DALYs) globally, by broad disease category, as of 2016

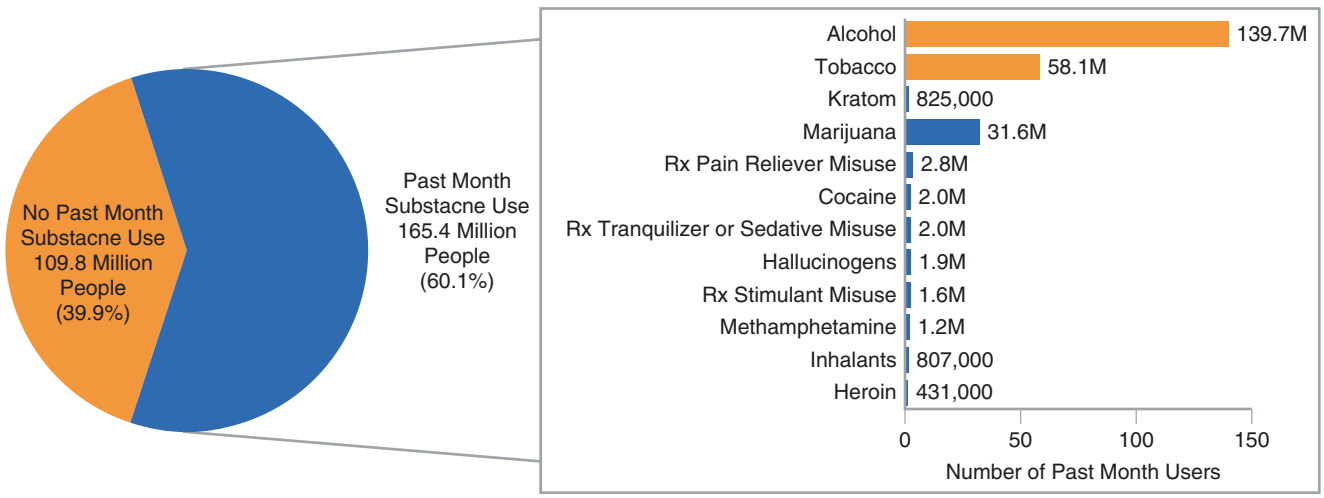


Fig. 14.4 Past month substance use among persons over the age of 12 in the United States in 2019

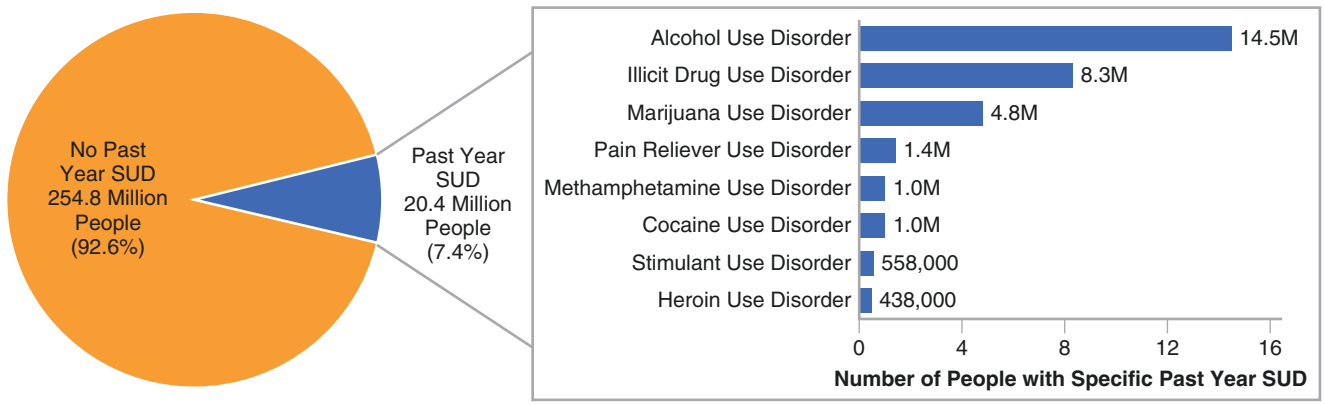


Fig. 14.5 Past year substance-use disorder among persons over the age of 12 in the United States in 2019

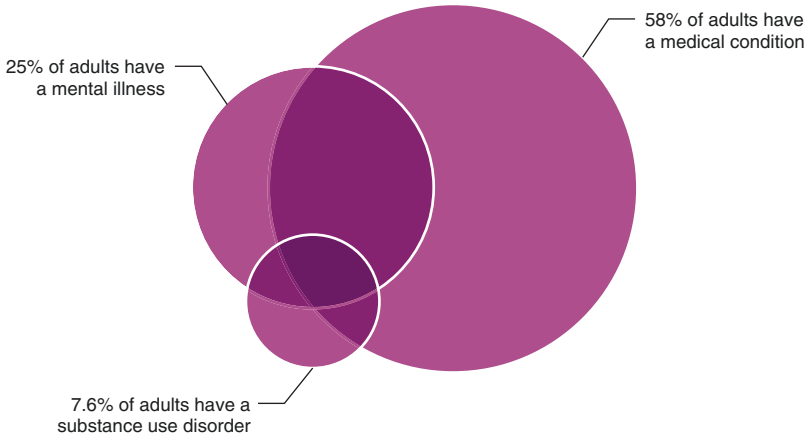


Fig. 14.6 Comorbidity of medical conditions, mental illness, and substance-use disorder in the United States

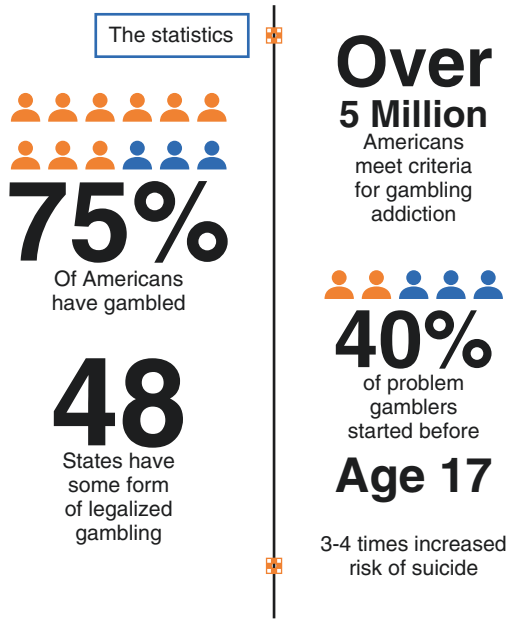


Fig. 14.7 Facts on gambling and gambling disorder in the United States

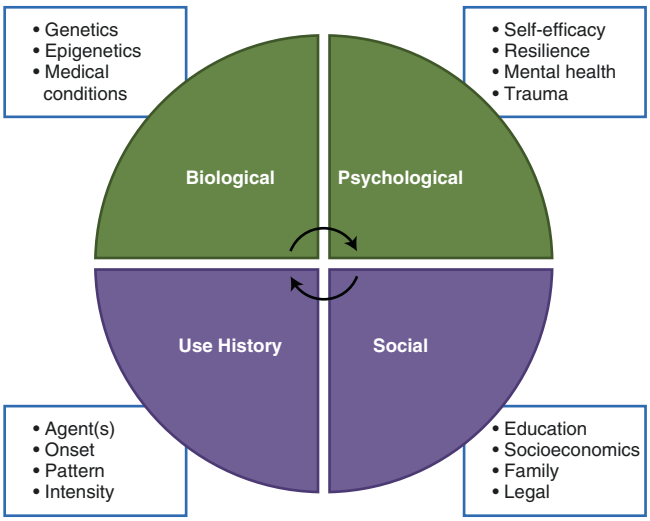


Fig. 14.8 Overview of the biological, psychological, social, and use factor domains that impact the development of a substance-use disorder

Approximately, 8.5 million adults (3.4%) had both a mental health condition and an alcohol or SUD in the past year. Among people with a SUD, 15 million (73%) had an alcohol use disorder, eight million (40%) had an illicit drug use disorder, and 2.7 million (13%) had both [5].

The lifetime prevalence of gambling disorder ranges globally between 0.2% and 2% depending on country and study, with a US average lifetime prevalence of 0.5% [6, 7]. According to the WHO, there are 350 million people worldwide who display problematic gambling behavior, with a 12-month prevalence of 0.1–5.8% [8]. As of 2015, over five million Americans met the criteria for gambling use disorder. Approximately two-thirds of persons with gambling disorder have a comorbid substance-use disorder, and gambling disorder is associated with an elevated risk of suicide attempts and completion (Fig. 14.7) [6].

Etiology

Substance-related and gambling disorders are paradigmatic biopsychosocial diseases. The etiology of these disorders encompasses complex interactions between biological factors (genetic vulnerability, physiological and behavioral responses to substance use, epigenetic changes to neurocircuits governing addiction), environmental factors (legality and criminalization, cultural perceptions, availability), psychological factors (personality traits such as novelty seeking), and substance factors (dose, route, biological action). Figure 14.8 summarizes the domains and factors that confer protective effects or vulnerability to substance-related and gambling disorders.

Genetics

Early family-based studies pointed to alcohol and other substance-use disorders clustering in families. Adoption

studies further demonstrated genetic predisposition, with the presence of SUD among biological parents associated with increased risk in their offspring regardless of the adoptive environment [9]. As shown in Fig. 14.9, large cohort studies of monozygotic twins have provided heritability estimates for several different substance-use disorders [11]. These ranges indicate a significant genetic contributor to substance-use disorders. For gambling disorder, familial and twin studies have reported a higher presence of gambling disorder in family members of individuals diagnosed with gambling disorder, with one study finding a lifetime prevalence of up to 20% of first-degree relatives [6].

Animal studies and different candidate gene association studies (CGAS) have implicated genes that underlie the neurobiology of substance-related disorders. For instance, underlying all substances with addiction potential is their ability to activate the brain's reward pathway and increase dopamine levels in the nucleus accumbens. In addition to dopamine, other neurotransmitters including serotonin, opioid peptides such as dynorphins, gamma-aminobutyric acid (GABA), acetylcholine, endocannabinoids, and glutamate also contribute to reward pathway activation [11]. Several of

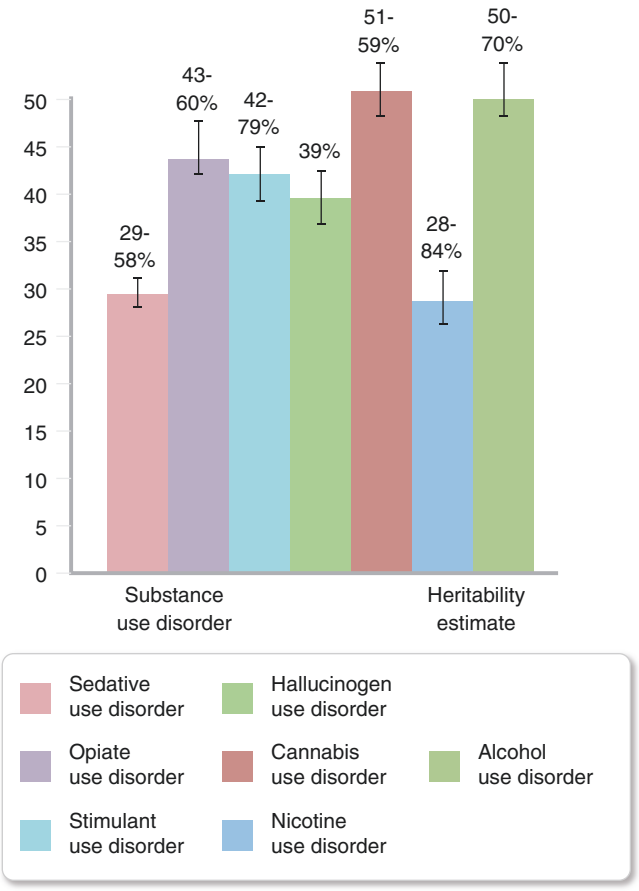


Fig. 14.9 Heritability estimates of substance-use disorders from monozygotic twin, adoption, and family studies. (Adapted from Ho et al. [10] with permission)

the genetic polymorphisms related to SUDs have also been linked to gambling disorder [6, 7]. Table 14.2 demonstrates a small sample of different genes implicated in various substance-related disorder phenotypes, including the involvement of different neurotransmitter systems and substance metabolism.

Neurodevelopment

Influencing the neurodevelopment of substance use and gambling behaviors are not only genetic polymorphisms but also epigenetic changes generated through early life stressors, such as insecure attachments; physical, emotional, and

Table 14.2 CGAS studies revealing genes implicated in substance-use disorder and gambling disorder phenotypes (Adapted from Ho et al. [10] with permission)

Target	Gene	Phenotype
Dopamine		
Receptors	*DRD2*	Smoking initiation, persistence, cigarette consumption, cessation
		Heroin use, cocaine use disorder
		Psychostimulant polysubstance-use disorder (mild)
		Alcoholism
	DRD3	Gambling disorder
	DRD4	Smoking risk, time to first cigarette, craving and response to smoking cues, nicotine use disorder
		Heroin, cocaine use disorder
		Methamphetamine use
		Gambling disorder
Transporters	*SLC6A3 (DAT1)*	Smoking risk
		Cocaine use disorder
Metabolism	*MAO-A*	Cigarette consumption, smoking risk, nicotine use disorder
		Gambling disorder
	TH	Smoking risk
	DBH	Smoking risk, nicotine use disorder
	COMT	Smoking risk, treatment response to nicotine spray and patch, nicotine use disorder
		Heroin, cocaine use disorder
		Alcohol use disorder
		Methamphetamine use
		Gambling disorder
Serotonin		
Transporters	*SLC6A4 (5HTT, SERT)*	Smoking risk, cigarette consumption, use disorder
		Alcohol use disorder
		Heroin use disorder
		Gambling disorder
Metabolism	*TPH1, 2*	Age of smoking initiation, risk of smoking
		Heroin use disorder
		Alcohol use disorder

Table 14.2 (continued)

Target	Gene	Phenotype
Receptor	*HTR2A*	Gambling disorder
Opioid		
Receptor (μ, δ, κ)	*OPRM1*	Heroin, opiate use disorder
		Alcohol use disorder
	OPRK1	Heroin, opiate use disorder
		Alcohol use disorder
	OPRD1	Heroin, cocaine use disorder
Acetylcholine		
Receptor	*CHRNA4*	Nicotine use disorder
	CHRNA5, A3, B4 gene cluster on chromosome 15	Nicotine use disorder, cigarette consumption, lung cancer, and COPD risk
		Alcohol, cocaine use disorder
Gamma-aminobutyric acid (GABA)		
Receptor	*GABRG2*	Heroin use disorder, methamphetamine use
	GABRA2	Alcohol use disorder
	GABBR2	Nicotine use disorder
Non-neurotransmitter enzyme targets		
Cytochrome P450 2A6	*CYP2A6*	Smoking risk, cigarette consumption, smoking cessation
Alcohol dehydrogenase 2	*ADH2, ADH4, ADH1B, ADH1C*	Alcohol use disorder
Aldehyde dehydrogenase 2	*ALDH2*	Alcohol use disorder
Cytochrome P450 2E1	*CYP2E1*	Alcohol use disorder

DRD2 D2 dopamine receptor; *DRD3* D3 dopamine receptor; *DRD4* D4 dopamine receptor; *SLC6A3 (DAT1)* dopamine transporter type 1; *MAO-A* monoamine oxidase A; *TH* tyrosine hydroxylase; *DBH* dopamine β hydroxylase; *COMT* catechol-*O*-methyltransferase; *SLC6A4 (5HTT, SERT)* serotonin transporter; *TPH1,2* tryptophan hydroxylase 1 and 2; *HTR2A* 2A serotonin receptor; *OPRM1/K1/D1* opioid receptor M1/K1/D1 subtypes; *CHRNA3/A4/A5/B4* nicotinic cholinergic receptor, α3, α4, α5, β4 subunit; *GABRG2* $GABA_A$ receptor, γ2 subunit; *GABRA2* $GABA_A$ receptor, α2 subunit; *GABBR2* $GABA_B$ receptor, subunit 2

sexual abuse; neglect; household instability; and poverty. These stressors lead to epigenetic changes that will alter circuits, influencing future substance use [12, 13]. Brain regions that are central to drug reward and reinforcement of behavior are part of the dopaminergic system [12, 14]. While dopaminergic circuits govern the robust drug reward response in substance use, recent publications review nondopaminergic circuits that also contribute to the development of substance-related disorders [14].

Figure 14.10 demonstrates the interconnectedness between the dopaminergic (DA) reward pathway, the hypothalamic–pituitary–adrenal (HPA) axis, and oxytocin (OT) circuits in the brain. Adverse childhood experiences lead to epigenetic changes in dopamine, oxytocin, and glucocorticoid production and receptor expression, which then changes brain reward pathways and how the brain responds to external cues. These alterations lead to higher-risk behaviors and development of mental health disorders that increase an individual's susceptibility to substance-use disorders [13].

The Dopamine Reward System

Figure 14.11 visualizes the main DA pathways in the brain. Most cerebral DA neurons are located in the ventral midbrain where the mesolimbic, mesocortical, and nigrostriatal DA systems begin. The mesolimbic DA system, known for its roles in reward and motivation, arises from the ventral tegmental area (VTA) and projects to the nucleus accumbens (NAc) (part of the ventral striatum) and amygdala (AMY); the mesocortical pathway projects from the VTA to the prefrontal cortex (PFC). The nigrostriatal DA system coordinates voluntary movement and regulates habit formation; it originates from the substantia nigra (SN) and projects to the dorsal striatum (DS) [14].

DA-related dysfunction has been associated with the pathophysiology of many psychiatric disorders, including depression, psychosis, substance-related, and gambling disorders. A growing body of research has established associations between early life experiences and DA changes. Figure 14.10 summarizes collated findings on dopaminergic changes at the molecular, neuroendocrine, and behavioral levels [6, 14].

The Hypothalamic–Pituitary–Adrenal Axis

The hypothalamic-pituitary-adrenal (HPA) axis governs the body's stress response and influences continued drug use, withdrawal, and relapse. Figure 14.12 outlines the HPA axis and its connection to the dopaminergic reward pathway. Stress activates the paraventricular nucleus (PVN) of the hypothalamus to release corticotropin-releasing factor (CRF). CRF binds to receptors in the pituitary to stimulate adrenocorticotropic hormone (ACTH) production [11]. ACTH is then transported to adrenal glands, leading to cortisol secretion. Once released, cortisol acts at glucocorticoid receptors (GRs) in the hypothalamus, pituitary, and hippocampus, to suppress further CRF and ACTH production (Fig. 14.12) [13]. The amygdala also produces CRF and mobilizes the HPA axis. Cortisol will stimulate the VTA, which leads to the activation of reward-seeking behaviors to mitigate stress (Fig. 14.12) [13].

As discussed below, in the withdrawal/negative affect stage of substance misuse, HPA axis dysregulation impacts SUD. Additionally, stress exposure precipitates substance use onset, decreases motivation to discontinue use, and enhances the risk of relapse [13]. The right column of Fig. 14.10 depicts how early childhood adversities increase HPA expression and stress sensitivity at a molecular level, leading to an individual's impaired capacity to respond effectively to stress and increasing susceptibility to substance use [13].

Oxytocin Pathways

Oxytocin's multiple functions are reflected in Fig. 14.13, which depicts modulatory interactions with systems impli-

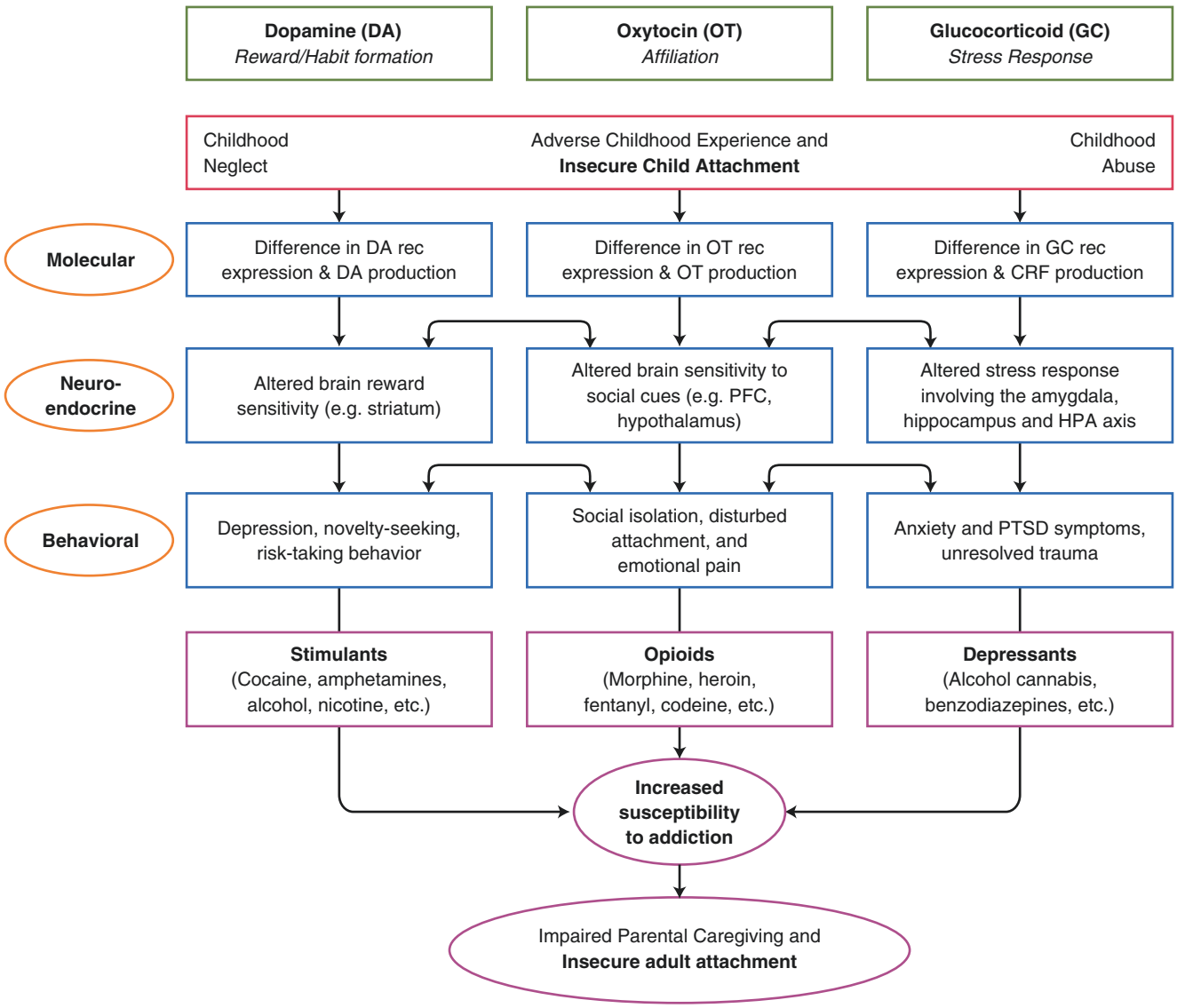


Fig. 14.10 Developmental and neurobiological pathways linking adverse childhood experience to susceptibility to addiction, due to modifications in the dopamine, oxytocin, and hypothalamic–pituitary–adrenal systems at molecular, neuroendocrine, and behavioral levels. *DA* dopamine; *OT* oxytocin; *GC* glucocorticoid; *rec* receptor; *CRF* corticotropin-releasing factor; *PFC* prefrontal cortex; *HPA* hypothalamic–pituitary–adrenal; *PTSD* post-traumatic stress disorder. (*Reproduced from* Strathearn et al. [13]; https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00737/full. Creative Commons Attribution License [CC BY 4.0])

cated in mood, stress, immune function, and addiction. Oxytocin is synthesized in the PVN and supraoptic nuclei. It is transported to the posterior pituitary gland. Oxytocin-producing neurons project to brain regions involved in social interactions, including the amygdala, ventral tegmental area, and the ventral striatum [13, 15].

As Fig. 14.13a demonstrates, oxytocin inhibits the HPA and dopamine reward systems. Studies have demonstrated oxytocin-mitigated inhibition of substance consumption, substance reward response, emotional impairments in withdrawal, and stress-induced relapse [15]. In early childhood adversity, all of the systems in Fig. 14.13 are dysregulated, including suboptimal development of the oxytocin system. As depicted in the middle column of Fig. 14.10, oxytocin dysfunction leads to changes in social behaviors that increase the risk of substance-use disorders [13, 15]. In early childhood adversity, the modulatory role of oxytocin on the other systems is also reduced. As oxytocin levels and reactivity are reduced, the negative feedback loops it regulates become dysfunctional. The associated outcome is an increased susceptibility to substance-related disorders through increased expression of dopaminergic and HPA systems, as seen in Fig. 14.13b [15].

Comorbidities with Personality, Psychiatric, and Medical Conditions

The genetic and epigenetic changes that alter different neurobiological systems not only impact vulnerability to

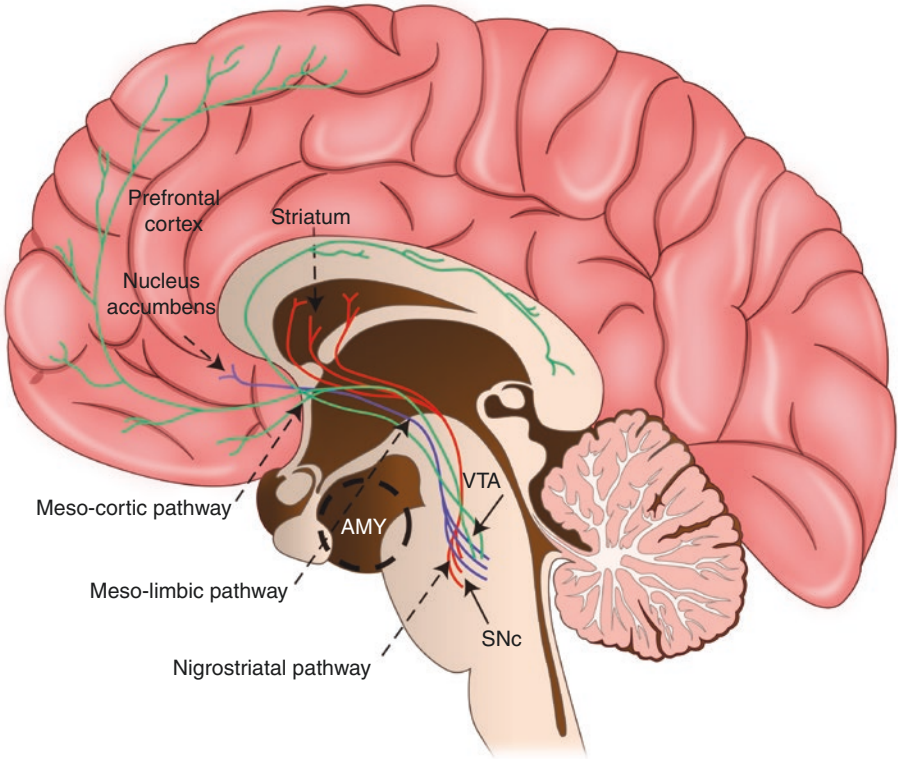


Fig. 14.11 Major dopaminergic pathways in the brain. *VTA* ventral tegmental area; SN_c substantia nigra pars compacta, *AMY* amygdala

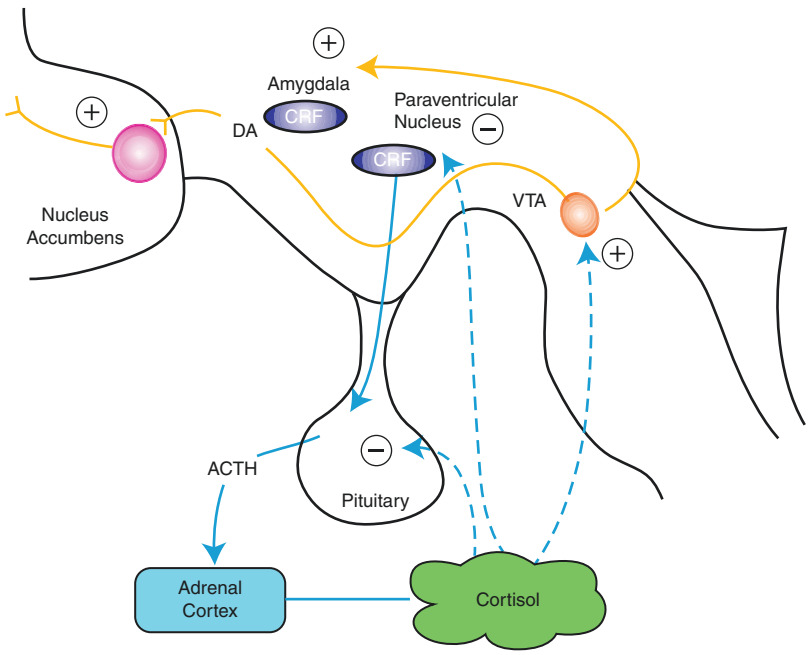


Fig. 14.12 The hypothalamic–pituitary–adrenal axis in relation to dopaminergic circuits. *CRF* cortico-tropin releasing factor; *ACTH* adrenocorticotropin hormone; *VTA* ventral tegmental area; *DA* dopamine

substance-related and gambling disorders but also influence an individual's development of personality traits, medical disorders, and psychiatric illness. In Fig. 14.14, genome-wide association studies (GWAS) mapped correlations between cigarette smoking and alcohol use parameters and various medical and psychiatric illnesses, with purple shading corresponding to negative correlations, orange to positive correlations, and intensity of color mapping to strength. The result was a network of interconnected correlations between alcohol- and nicotine-related behavior and a multitude of comorbidities [16].

Personality Traits

Figure 14.15 depicts three studied systems of personality.

Image (A) depicts the positive emotionality/extroversion (PEM/E) personality trait, which correlates with increased

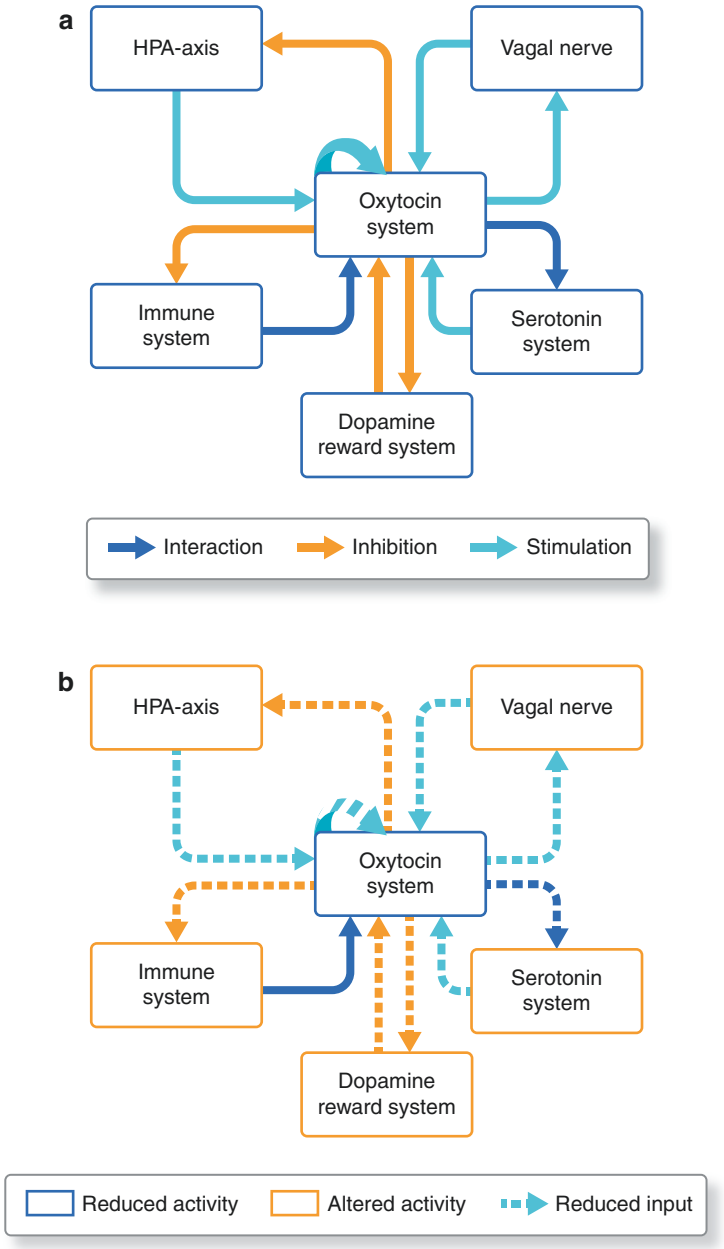


Fig. 14.13 Bidirectional interactions between oxytocin and other systems implicated in addiction. Note that only oxytocin, HPA-axis, and dopamine reward system discussed in detail in this chapter. *HPA* hypothalamic–pituitary–adrenal axis. (*Reproduced from* Bowen et al. [15]; *with permission*)

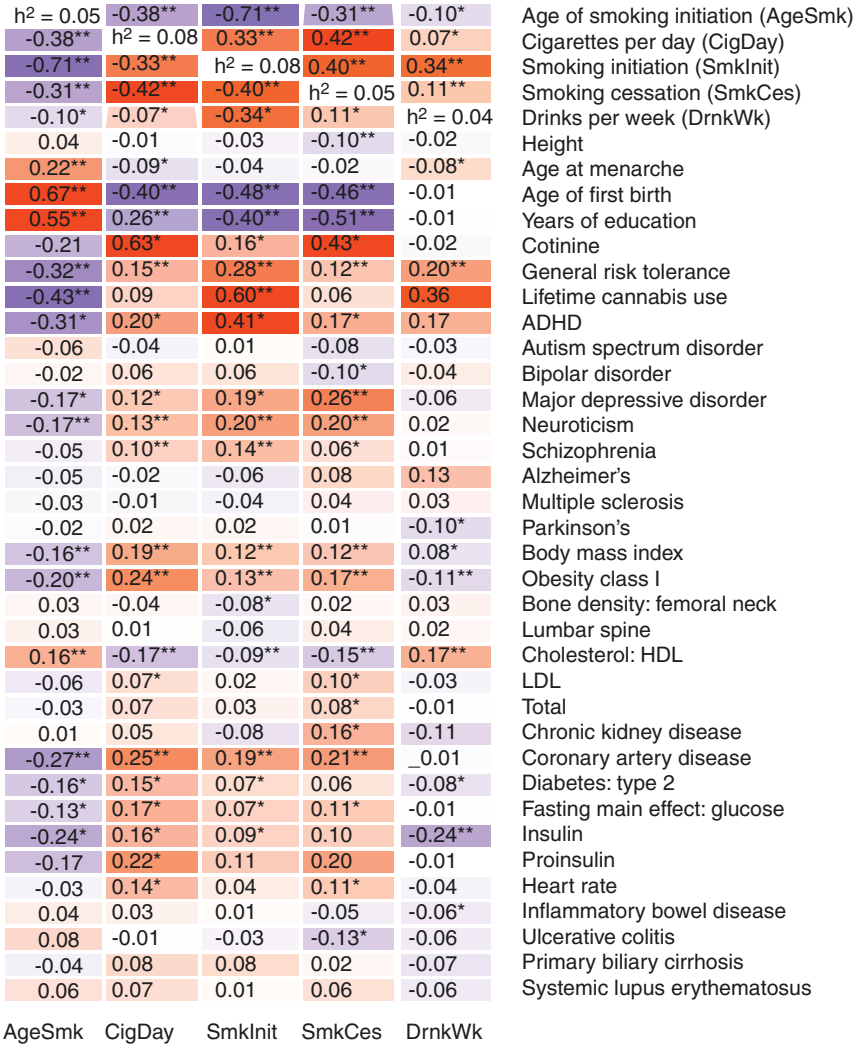


Fig. 14.14 Summary of GWAS studies correlations with cigarettes and alcohol markers and chronic physical and mental disorders. (*Reproduced from* Liu et al. [16]; *with permission*)

reward sensitivity, demonstrated as positive affect, strong motivation, desire, enthusiasm, and optimism. The PEM/E personality is modulated by the dopaminergic systems previously discussed and connected to changes in the D2 receptor gene, and in studies, high PEM/E expression decreases the risk of SUD development and low PEM/E increases risk [17]. The blue arrows indicate the PEM/E brain system, with circuits from the ascending dopaminergic system originating from the mesencephalon and innervating the striatum, rostral anterior cingulate (rACC) cortex, and ventromedial prefrontal cortex.

Image (B) depicts the negative emotionality/neuroticism (NEM/N) personality trait, which represents underlying sensitivity to punishment and stress signals. Individuals with high NEM/N are more likely to have anger, anxiety, guilt, and depression. The NEM/N trait is modulated by connections between the frontal cortex and the amygdala. Individuals with high NEM/N have decreased prefrontal control over the amygdala, which increases substance-use risk [17]. The green arrows indicate the NEM/N system, with glutamatergic outputs from the rACC and vmPFC to the amygdala and insula (insula not shown).

Image (C) depicts the constraint (CON) personality trait, which is thought to be a more complex personality expression that encompasses behavioral restraint via intentional and volitional control versus impulsivity, and as such involves more complex circuits in the brain. Low CON in studies is consistently associated with SUD [17]. The green arrows indicate the CON brain system, with circuits from the pre-supplementary motor area (preSMA) and right inferior frontal gyrus (rIFG) to the striatum and the subthalamic nucleus (STN).

Psychiatric and Medical Comorbidities

Multiple national population surveys have found that about half of those who experience a mental illness during their lives will also experience a SUD and vice versa [5]. Figure 14.16, taken from the 2019 NSDUH survey, shows

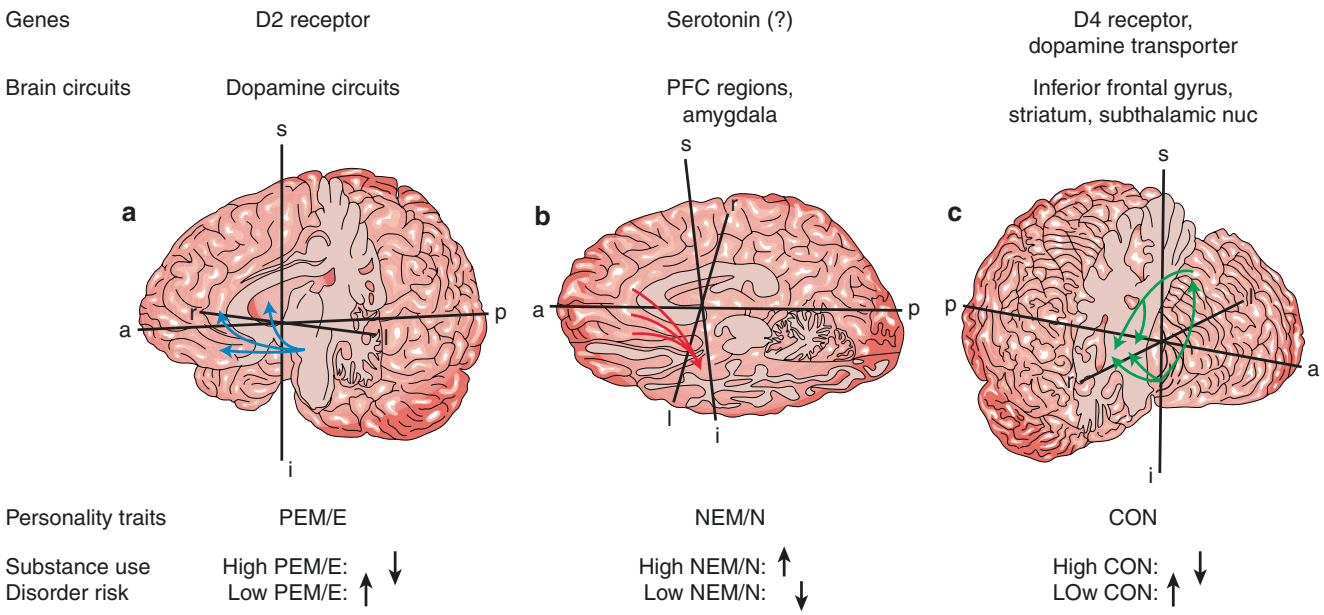


Fig. 14.15 Genes and correlated brain systems involved in the phenotypic expression of personality traits, *PFC* prefrontal cortex; *PEM/E* positive emotionality/extroversion; *NEM/N* negative emotionality/neuroticism; *CON* constraint. (*Adapted from* Belcher et al. [17]; *with permission*). The arrows indicate major input and output regions (see text) for the involved brain systems

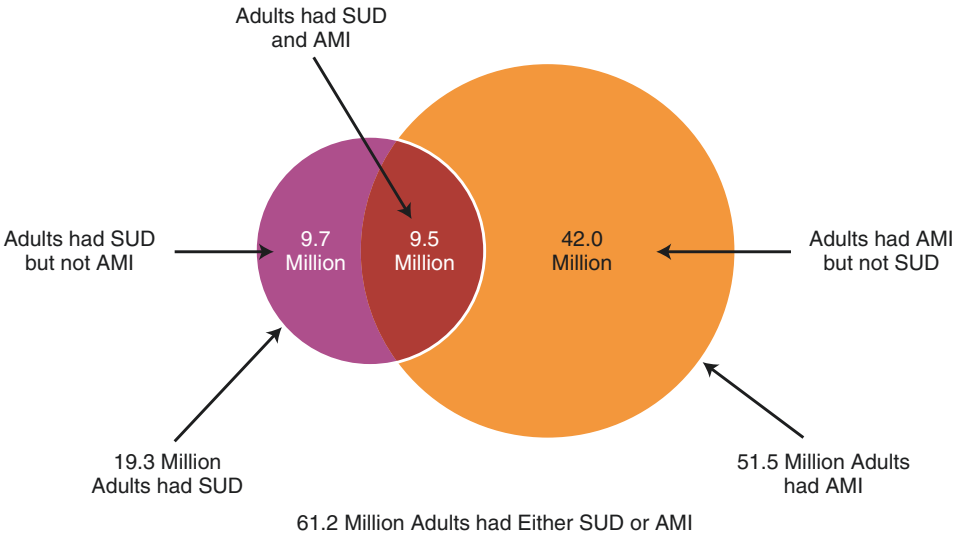


Fig. 14.16 Past year substance-use disorder (SUD) and mental illness among adults aged 18 or older in 2019 [5]. SUD, substance-use disorder

that out of 61.2 million adults who had either SUD or a mental illness diagnosis, 9.5 million people experienced both [4]. Reciprocal co-occurrence, as demonstrated in Fig. 14.16, is hypothesized to occur due to (1) overlapping genetic, neurobiological, developmental, and environmental influences, (2) increased risk of substance use as a way to self-medicate a mental illness, and/or mental illness and neurological changes increase substance use propensity, and (3) substance use may alter neural pathways that increase a person's propensity to develop a mental illness [5, 9].

In the US National Comorbidity Survey Replication study, 96% of individuals with disordered gambling were estimated to have one or more psychiatric disorder and 64% have been estimated to have three or more psychiatric disorders [6]. As seen in Fig. 14.17, major comorbidities included substance-use disorders, anxiety and trauma disorders, mood disorders, and impulse control disorders [6].

Figure 14.18 demonstrates that patients with SUD had a higher prevalence of 19 major health problems. Chronic pain, chronic obstructive pulmonary disease, congestive heart failure, and hepatitis C are among the most elevated prevalence. Patients with SUD also had a heightened 10-year mortality risk. Patients with opioid use disorder exhibited the highest elevation in 10-year mortality risk, with average disease-burden scores that were nearly twice as high as patients without opioid use disorder [18].

The reciprocal co-occurrence between SUD and medical disorders is due to direct damaging effects of the substances themselves on target organs (i.e., alcohol and hepatic cirrhosis or nicotine inhalation and lung diseases), consequences of the method of use (i.e., HIV and hepatitis C and injectable substances), links between mental illness, substance use, and decreased self-care, and epigenetic impacts of early adversity not only on substance use but also on the risk for concurrent physical illnesses (i.e., chronic pain, heart disease, diabetes [18, 19]).

Social and Structural Determinants

Figure 14.19 models the complex interaction between physical, economic, and sociocultural factors that contribute to substance use and gambling patterns and consequences [6, 20]. These social and structural determinants influence behavioral patterns but also shape how attitudes and policies impact the treatment of these disorders.

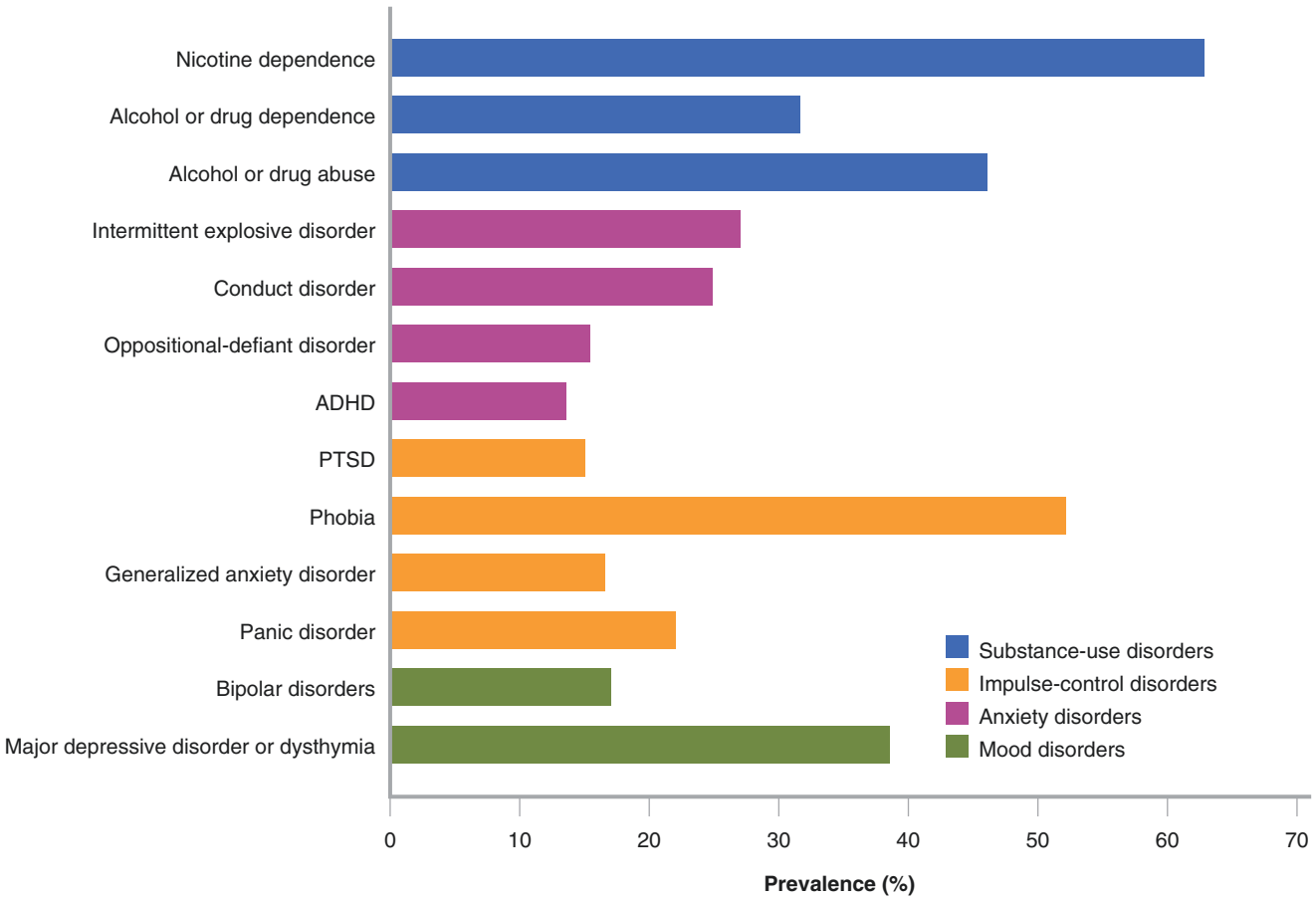


Fig. 14.17 Percent prevalence of substance-use disorders and mental health conditions co-occurring gambling disorder. (Data from the National Comorbidity Survey Replication; reproduced from Potenza et al. [6]; *with permission*)

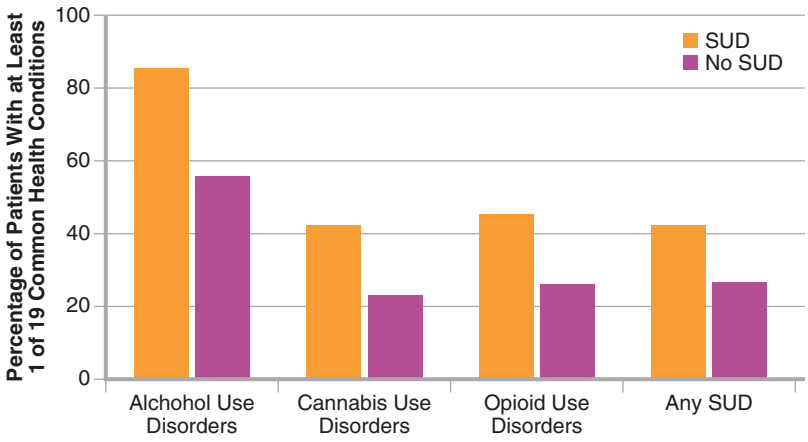


Fig. 14.18 Prevalence of major health problems co-occurring with substance-use disorders

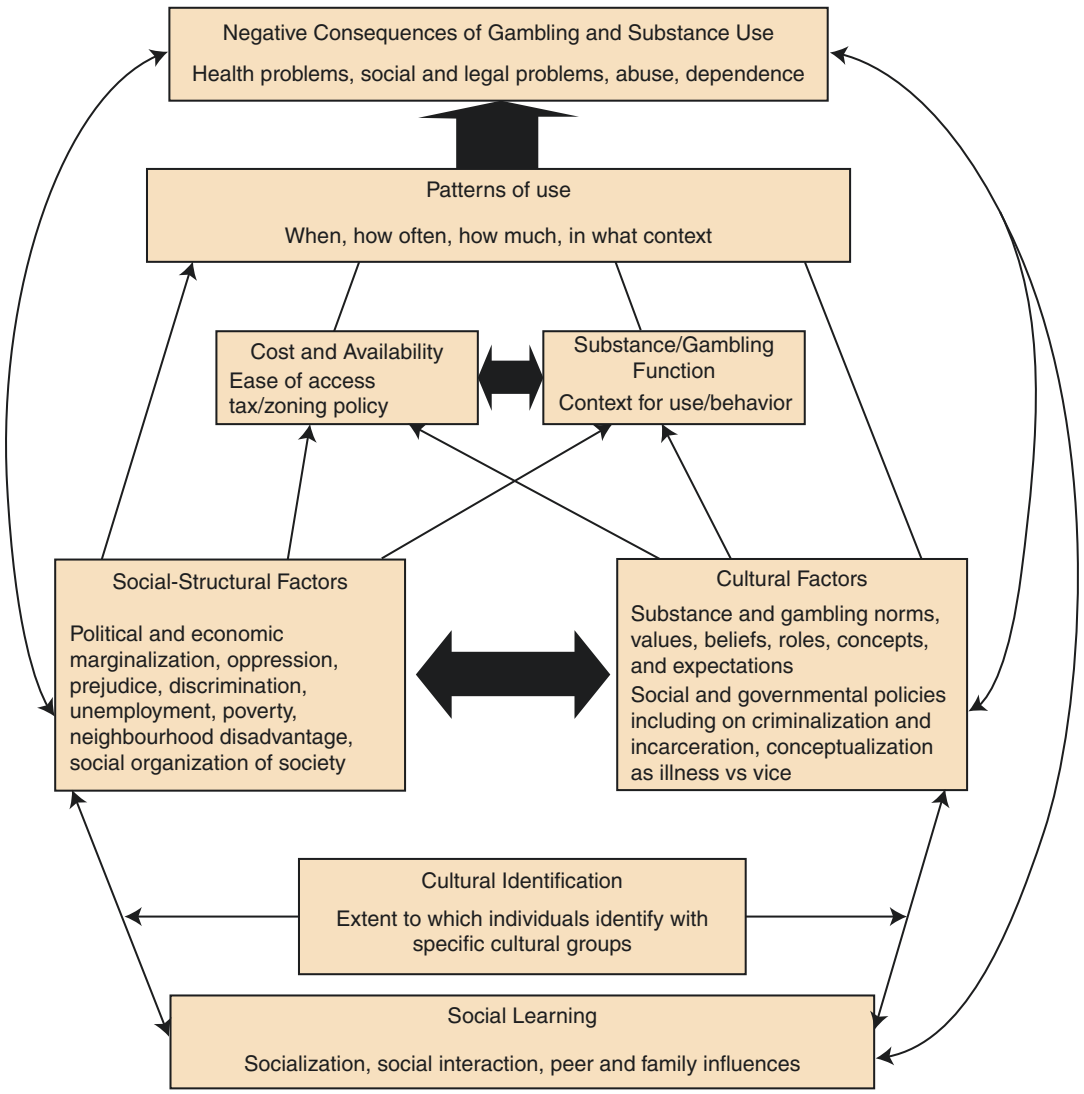


Fig. 14.19 Social and structural determinants contributing to the risk of developing a substance use or gambling disorder

There is budding research studying how structural vulnerabilities impact different stages of substance use and gambling disorders. In one study, increased illicit opiate and stimulant use in a population of HIV-positive women was associated with discrimination/stigma, economic hardship, and a summation of multiple adversities [21]. In another

study, low rates of treatment for Hispanic men with alcohol use disorder mapped to poor access, lack of culturally and linguistically appropriate treatment, lack of cultural and community awareness and stigmatization, and education [22]. A study surveying US adults nationally found that adults living in disadvantaged neighborhoods and with lower educational status had higher rates of gambling disorder [23]. Thus, these environmental factors become just as important and complex in shaping the stages of substance misuse as an individual's biological underpinnings.

Pathophysiology

Stages of Substance Misuse and Gambling Leading to Substance-Related and Gambling Disorders

As Fig. 14.20 illustrates, substance-use and gambling disorders begin with an initial exposure and an associated reward response. The reward signaling in the brain positively reinforces substance use and/or gambling. Repeat stimulus/reward and positive reinforcement lead to an individual associating the addictive substance or gambling behavior—including its places, items, emotional states, and people—with an incentivized positive stimulus. This phenomenon, known as incentive salience, motivates the individual to continue substance use. Over time, an individual loses their ability to control their behavior. With continued use, neuroadaptations occur, the reward signals and positive reinforcement decrease, and the expression of stress systems increases. The negative emotional and physical states of substance withdrawal lead to negative reinforcement of continued use and eventually to dependence [12, 14]. Research on gambling disorder suggests a similar pattern of initial conditioning stimuli to perpetuate gambling use and reward impulsive behaviors, with decreased changes in reward signaling over time and stress dysregulation [6].

The pathophysiology of substance-related and gambling disorders is conceptualized in three stages of an ever-worsening cycle, which include the binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation stages (Fig. 14.21). In the binge/intoxication stage, an individual consumes an intoxicating substance or engages in gambling behaviors and experiences the pleasurable reward that reinforces use. In the withdrawal/negative affect stage, the individual will experience a negative physical and emotional state without the substance/gambling behavior, and in the preoccupation/anticipation stage, the individual feels compelled to use the substance/gamble again after a period of abstinence [6, 12, 14].

There are at least 18 discrete neuro-circuits in the brain that mediate these pathophysiologic stages [14]. The three major brain regions involved in the development and persistence of SUD and gambling disorders are the basal ganglia, the amygdala and its extended structures, and the prefrontal cortex (Fig. 14.21) [6, 12, 14]. The major neurotransmitters and structures involved in the various stages are discussed here.

Neuroanatomy

The ventral tegmental area and basal ganglia structures, including the nucleus accumbens and dorsal striatum (DS), are discussed in the section on the dopaminergic pathways (Fig. 14.11) [14].

The extended amygdala, including the amygdala (CeA), and the bed nucleus of the stria terminalis (BNST) regulate

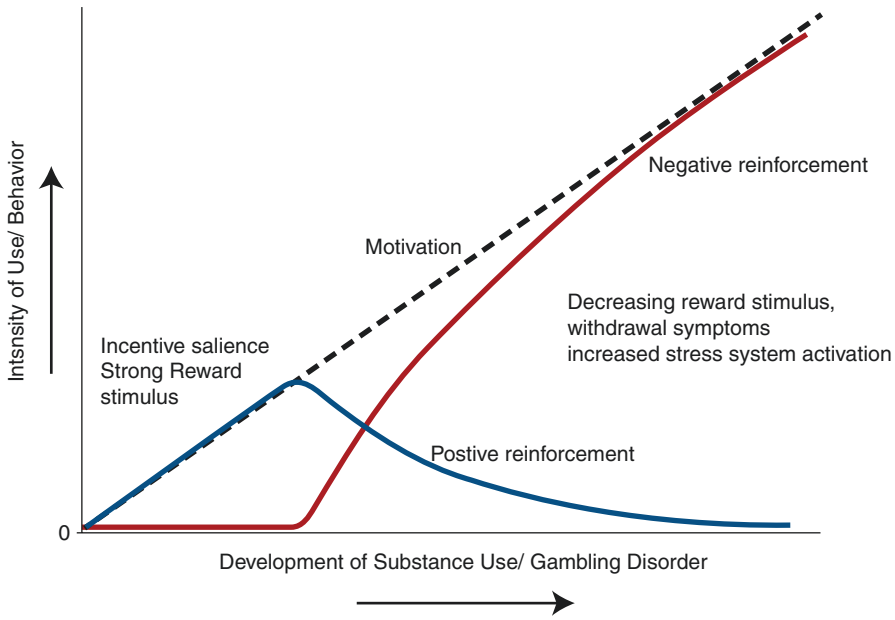


Fig. 14.20 Transition from positive to negative reinforcement in the development of a substance-use disorder

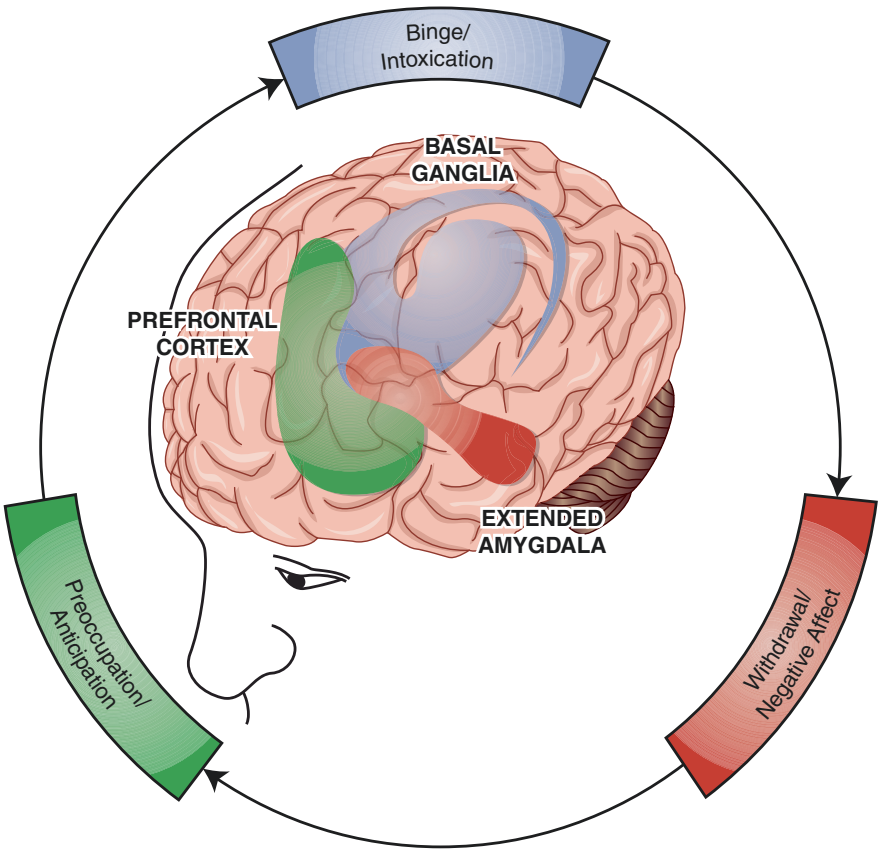


Fig. 14.21 The three stages and major brain regions involved in the substance and gambling misuse cycle

the brain's stress response and associated behavioral and emotional responses to stress (Fig. 14.21). As part of the stress circuitry, the extended amygdala has connections to the hippocampus to influence memory formation around substance use and the hypothalamus to activate the HPA axis and regulate cortisol release. The extended amygdala's functions play a role both initially in incentive salience and positive reinforcement but also in the negative reinforcement and withdrawal aspects of the misuse cycle leading to habituation and dependence [12, 14, 24].

The prefrontal cortex (PFC) (Fig. 14.21) is responsible for complex cognitive functions, including organization and prioritization of thoughts, activities, and behaviors; time management; complex decision-making; and regulation of action, emotions, and impulses. In substance use and gambling, the structures of the PFC (including the anterior cingulate cortex, the medial-orbitofrontal cortex, and the ventrolateral PFC) initially exert inhibitory control over substance use, but these circuits are downregulated with repeated, excess use [6, 12, 14].

Binge/Intoxication Stage

The main neuroanatomical structures and circuits involved in the binge intoxication stage are demonstrated in Fig. 14.22. Imaging studies such as Fig. 14.23 demonstrate that intoxicating doses of alcohol and drugs, as well as repeated wins and near-losses in gambling, release dopamine and opioid peptides from the VTA either directly or indirectly into the nucleus accumbens [6, 12, 14]. Dopaminergic projections from the VTA to the extended amygdala, the hippocampus, and insula create the positive emotional affiliations that lend to incentive salience (Fig. 14.22).

As Fig. 14.24 demonstrates, intoxicating substances lead to a much higher release of dopamine in the synapses of the reward pathway than natural rewards, encouraging repeat use to obtain a greater reward stimulus. Projections to the dorsal striatum (DS) encourage substance- and gambling-seeking behaviors; repeat DS signaling leads to habit formation and contributes to compulsive use (Figs. 14.11 and 14.22) [6, 12, 14]. While the prefrontal cortex provides inhibitory control to the basal ganglia and the extended amygdala through inhibitory gamma-aminobutyric acid (GABA) projections, these inhibitory signals begin to weaken as repeated stimulation of the reward circuits strengthen the incentive salience of the substance [6, 12, 14, 25] (Fig. 14.22, PFC projections).

Withdrawal/Negative Affect Stage

With chronic substance exposure, there are changes in the reward pathways that lead to diminished reward responses; in particular, decreased dopaminergic transmission in the nucleus accumbens and decrease opioid peptide signalling leads to decreased reward experience [6, 12, 14, 25] (Fig. 14.22). These changes in dopaminergic signaling

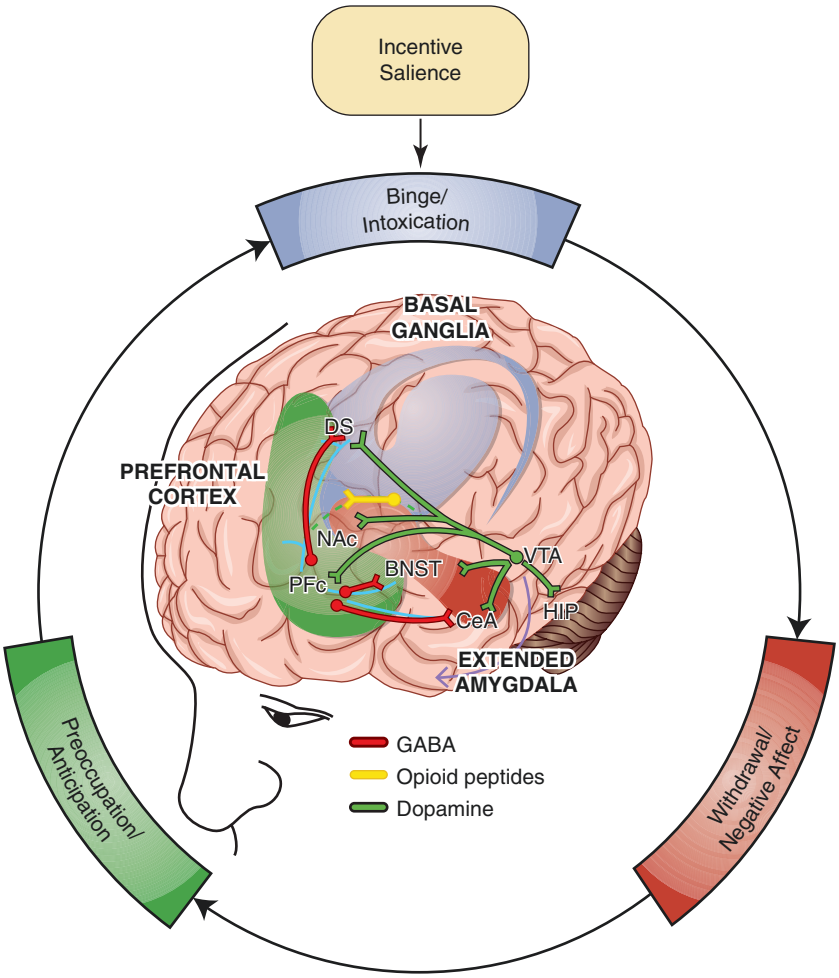


Fig. 14.22 Positive reward reinforcement and increased incentive salience in the binge/intoxication phase. *PFC* prefrontal cortex; *DS* dorsal striatum; *Nac* nucleus accumbens; *BNST* bed nucleus of the stria terminalis; *CeA* amygdala; *Hyp* hypothalamus; *VTA* ventral tegmental area; *HIP* hippocampus

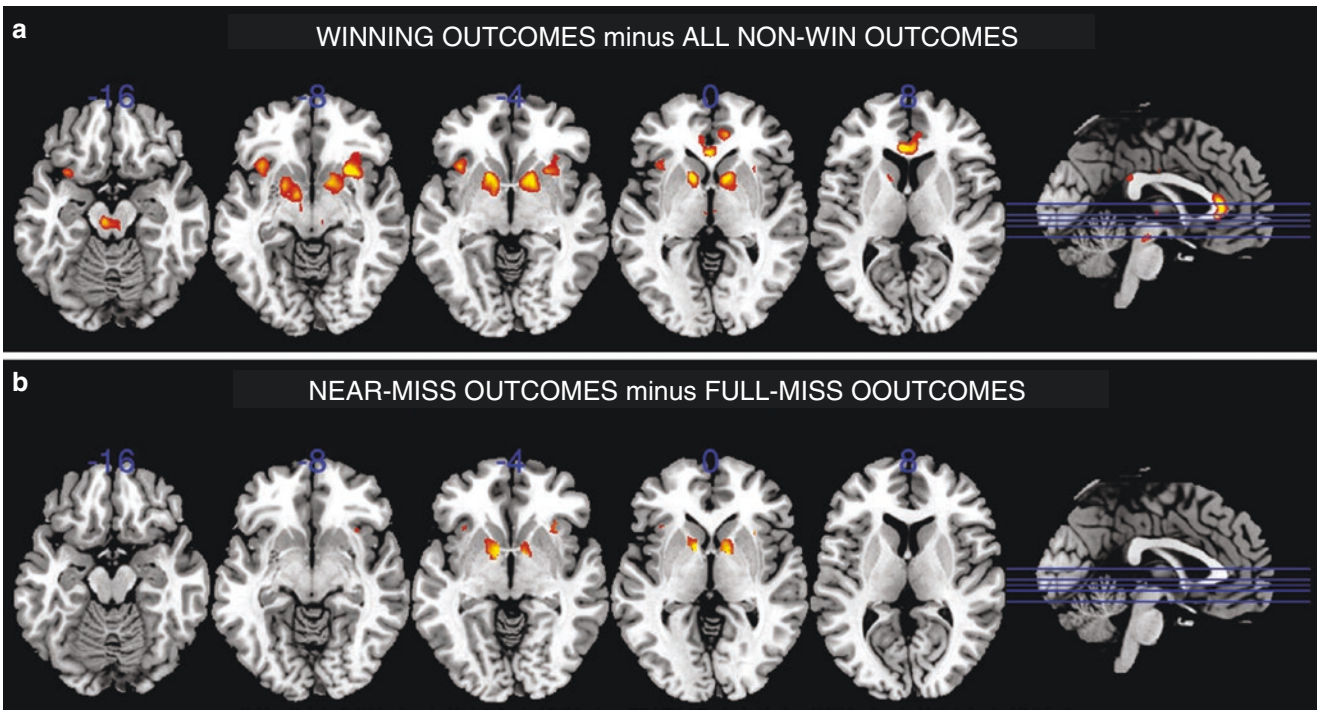


Fig. 14.23 Neural activity to winning and near-miss outcomes. (**a**) Neural responses to monetary wins compared to all non-wins, modeled to the onset of the outcome phase, with significant win-related activity in the striatum, ventral tegmental area, anterior insula, and prefrontal cortex (anterior cingulate). (**b**) Neural responses to near-miss compared to full miss outcomes, with significant activity in the bilateral striatum and anterior insula. (*Reproduced from* Clark [32]; https://doi.org/10.1016/j.neuron.2008.12.031. [CC BY 3.0])

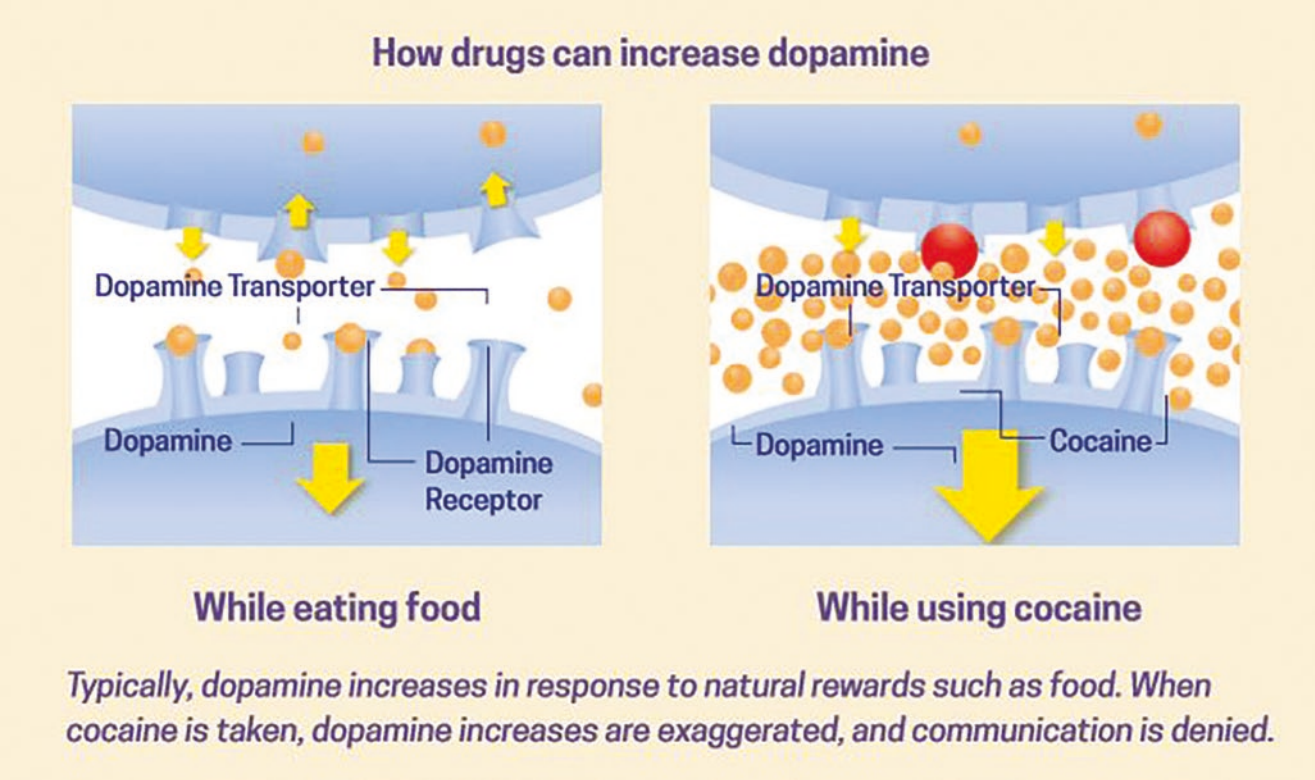


Fig. 14.24 Dopamine release in reward circuitry with food/other natural reward stimulus vs intoxicating substance or gambling (example of cocaine). (*Reproduced from* Ambre et al. [33]; *with permission*)

include a decrease in the expression of D2 receptors in reward circuitry. Figure 14.25 demonstrates changes in D2 dopamine receptors in the basal ganglia with repeated substance exposure. Studies of gambling disorder show decreased activation of the ventral striatum (nucleus accumbens) in response to gambling regard, which mirrors decreased activation of the reward circuitry in substance-use disorder at this stage [6, 14].

The emotional dysregulation associated with the withdrawal/negative affect stage involves the HPA axis and brain stress system. These systems, mediated by corticotropin-releasing factor (CRF), norepinephrine, and dynorphins, are recruited and then dysregulated by chronic exposure to gambling or a substance of abuse leading to increased HPA and central stress system expression in the extended amygdala (Fig. 14.26) [6, 12, 14].

Thus, an individual experiences both increased irritability and negative emotional states and decreased pleasure responses at baseline, with heightened negative and physical states in withdrawal and abstinence, known as "stress surfeit" [12, 14]. Thus, motivation increases to escalate substance use to regain the pleasurable effect, which becomes increasingly difficult to experience, but also to avoid uncomfortable withdrawal, leading to negative reinforcement of substance use and gambling behaviors (Fig. 14.20).

Preoccupation/Anticipation Stage

In the preoccupation/anticipation stage, an individual experiences craving and substance/gambling-seeking impulses during a period of abstinence. These drives are generated by increases in habitual behavior and incentive through reinforced circuits to the dorsal striatum, extended amygdala, and hippocampus, and negative reinforcement through stress-system expression, all of which lead to chronic down-regulation of executive function control over substance use behavior [6, 12, 14] (Fig. 14.27). As seen in the PET imaging in Fig. 14.28, decreased brain metabolism in regions of the prefrontal cortex reflects the decrease in behavioral regulation of the PFC that occurs with chronic use of intoxicating substances.

With respect to the activity of neurotransmitters, there is prominent dysregulation of glutamate, the brain's primary excitatory neurotransmitter that drives actions/response throughout the brain, and GABA, the brain's primary inhibitory neurotransmitter that regulates the expression and prioritization of behavior. GABA also regulates the HPA axis, the brain's stress systems, the extended amygdala, and reward circuitry [6, 12, 14]. In chronic substance use and disordered gambling, there is a disruption in both glutamate and GABA signaling in the prefrontal cortex and throughout the brain, leading to executive function deficits

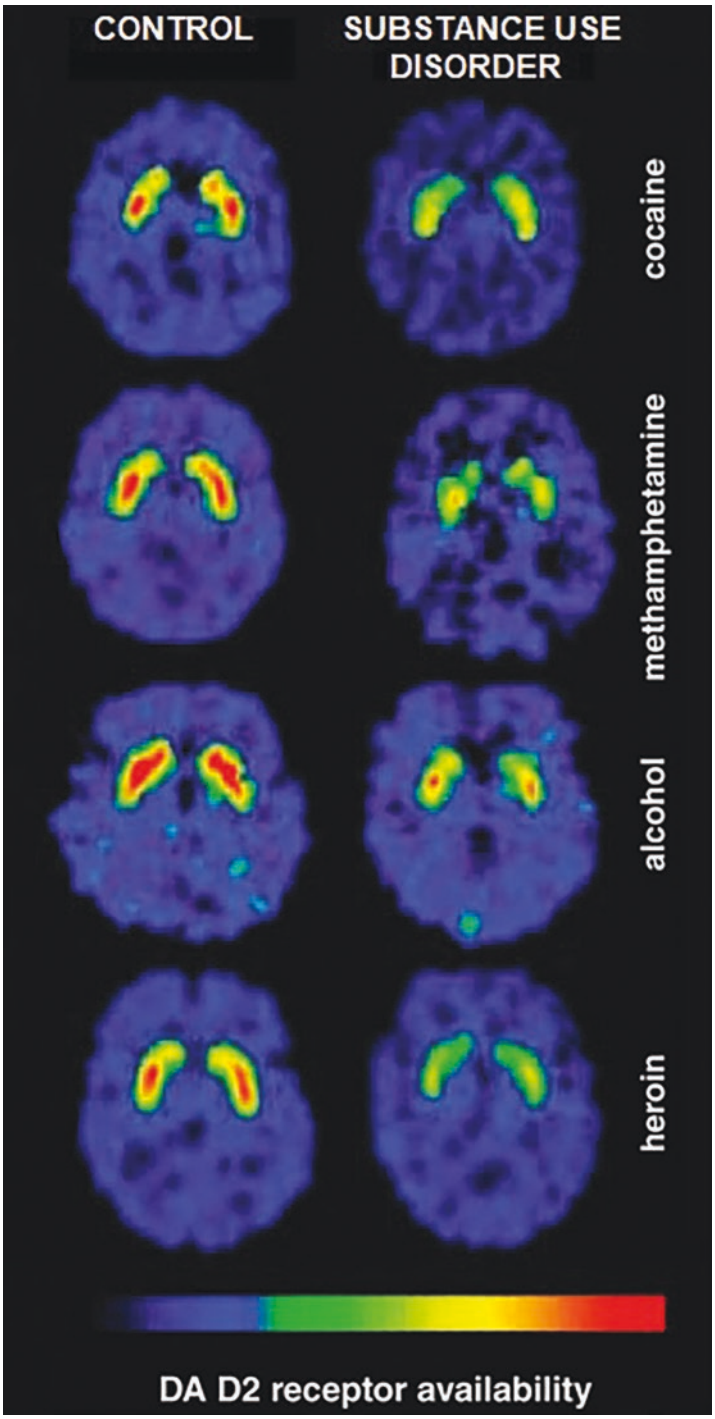


Fig. 14.25 Decreased D2 dopamine receptor expression in patients with various substance-use disorders as compared with controls. (*Adapted from* Volkow et al. [34]; *with permission*)

in the control of disordered behaviors and reactions (Fig. 14.27). The over-activation of glutamate in the prefrontal cortex promotes craving as impulsive/compulsive substance seeking, and over-activation throughout the brain leads to worsening of withdrawal/negative affect stage, encouraging relapse and return to the binge/intoxication stage [6, 12, 14].

Phenomenology

Table 14.3 presents the DSM-5 criteria for substance-use disorders, two of the substance-induced disorders—substance intoxication and substance withdrawal—and gambling disorder. Tolerance and withdrawal alone do not establish a diagnosis of SUD, and if a substance is prescribed

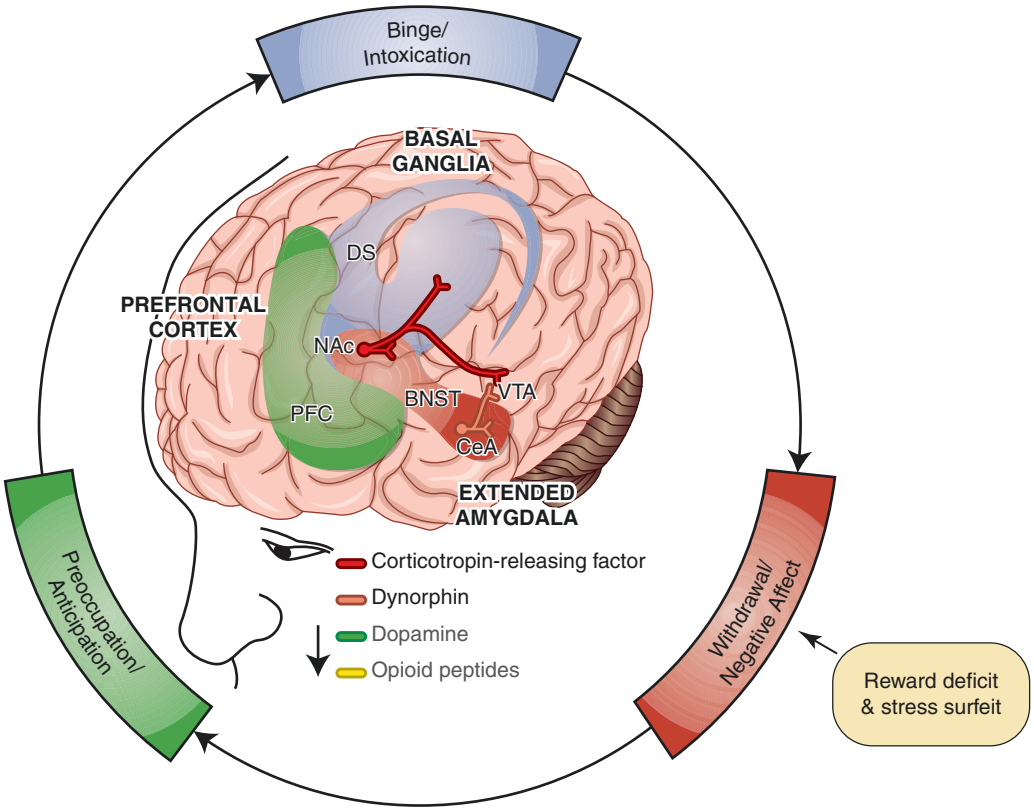


Fig. 14.26 Decreased reward and increased stress response in the withdrawal/negative affect stage. *PFC* prefrontal cortex; *DS* dorsal striatum; *Nac* nucleus accumbens, *BNST* bed nucleus of the stria terminalis; *CeA* amygdala; *Hyp* hypothalamus; *VTA* ventral tegmental area

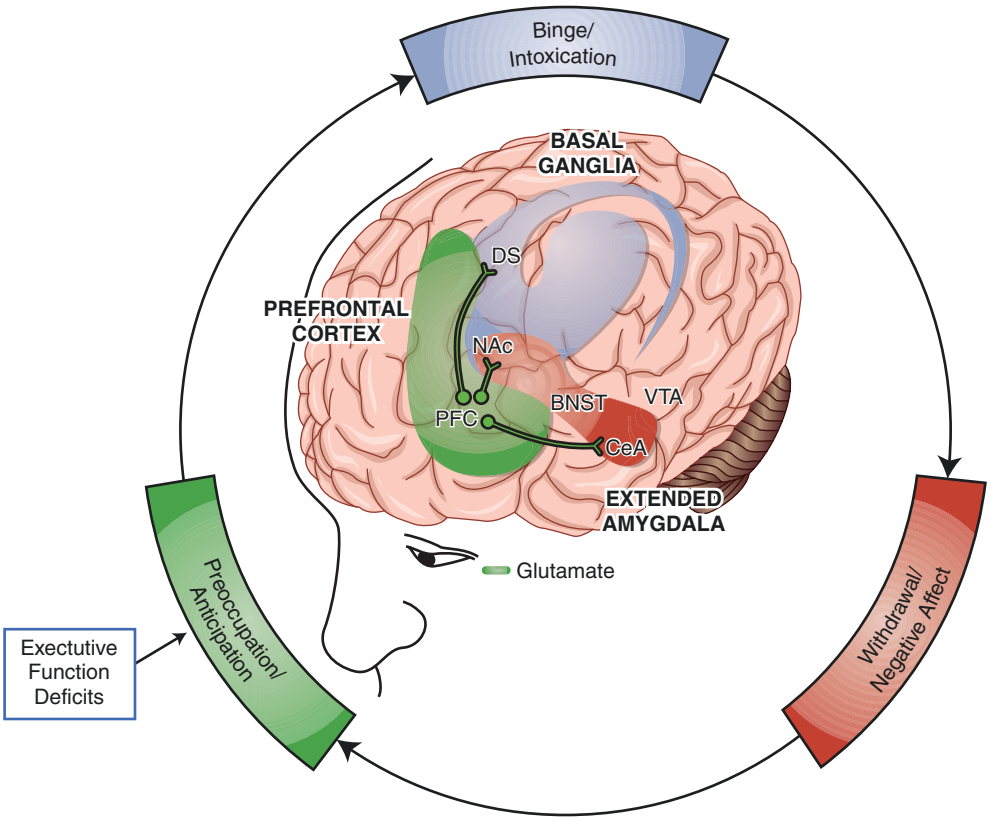


Fig. 14.27 Increased craving, compulsive use, and decreased control in preoccupation/anticipation stage. *PFC* prefrontal cortex; *DS* dorsal striatum; *Nac* nucleus accumbens; *BNST* bed nucleus of the stria terminalis; *CeA* amygdala; *VTA* ventral tegmental area

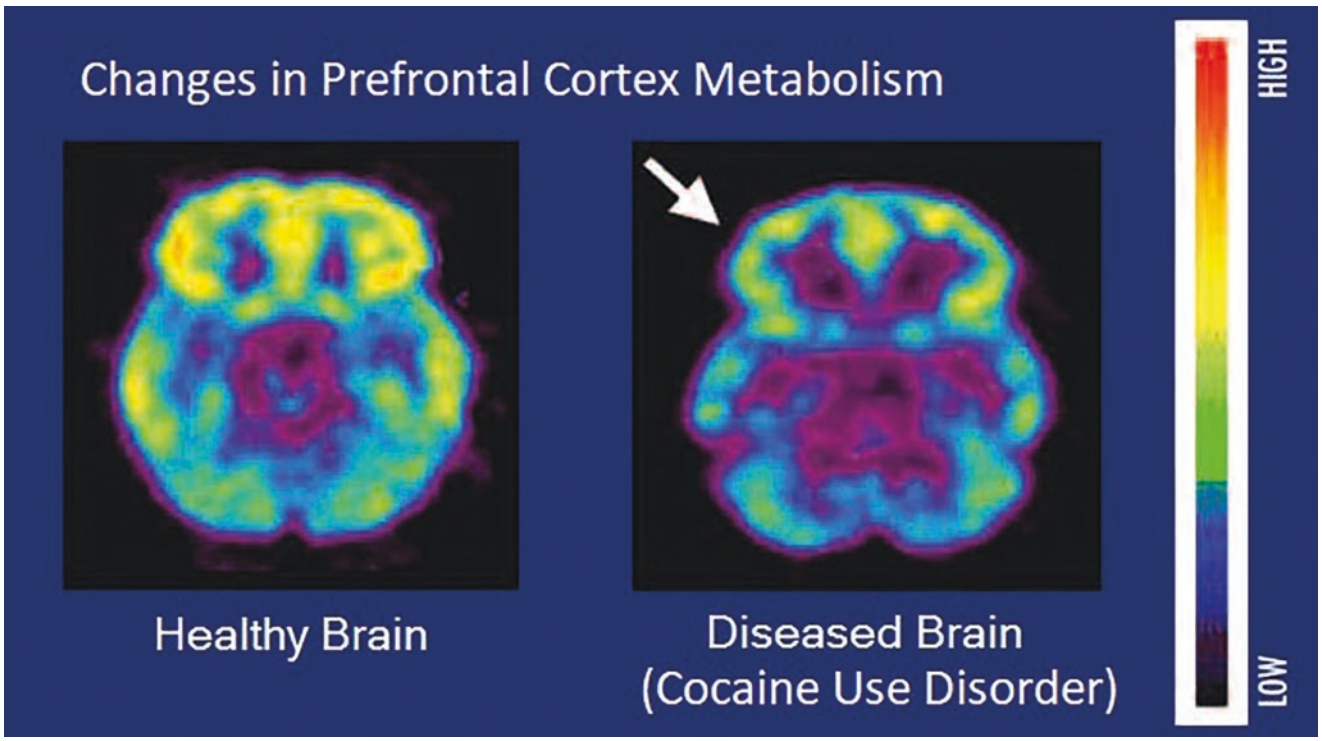


Fig. 14.28 Decrease in regional brain metabolism in the orbital frontal cortex, control vs cocainse use disorder. (*Adapted from* Volkow et al. [34]; *with permission*)

Table 14.3 DSM-5 criteria for substance use, disorders, substance-induced disorders, and gambling disorder

Substance-use disorder	
A. A problematic pattern of substance use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period: 1. Use in larger amounts or over a longer period than was intended 2. Persistent desire or unsuccessful effort to cut back or control use 3. A great deal of time is spent in activities necessary to obtain, use, or recover effects 4. Cravings or persistent desire to use 5. Failure to fulfill major role obligations at work, school, or home 6. Persistent use despite recurrent social or interpersonal problems 7. Important social, occupational, or recreational activities are given up or reduced 8. Recurrent use in situations in which it is physically hazardous 9. Persistent use despite knowledge of physical or psychological problems caused or exacerbated by using 10. Tolerance 11. Withdrawal (refer to Criteria A and B of the criteria set for cannabis withdrawal)	
Substance-induced disorders (substance-induced psychiatric disorders covered in other sections)	
Substance intoxication	**Substance withdrawal**
A. Recent use of substance B. Clinically significant problematic behavioral or psychological changes (e.g., inappropriate behavior, mood lability, impaired sensory-motor function, impaired judgment) that developed during, or shortly after, substance use C. One (or more) substance-specific signs or symptoms developing during or shortly after use (e.g., incoordination; altered speech; impaired cognition; altered vital signs; altered arousal) 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	A. Cessation of substance use that has been heavy and prolonged B. Two (or more) substance-specific signs and symptoms develop within approximately 1 week after Criterion A: (e.g., autonomic hyperactivity; tremor; insomnia; perceptual disturbances; affective dysregulation; seizures…) 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 or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance

(continued)

Table 14.3 (continued)

Substance-use disorder
Gambling disorder
A. Persistent and recurrent problematic gambling behavior leading to clinically significant impairment or distress, as indicated by the individual exhibiting four (or more) of the following in a 12-month period: 1. Needs to gamble with increasing amounts of money in order to achieve the desired excitement 2. Is restless or irritable when attempting to cut down or stop gambling 3. Has made repeated unsuccessful efforts to control, cut back, or stop gambling 4. Is often preoccupied with gambling (e.g., having persistent thoughts of reliving past gambling experiences, handicapping or planning the next venture, thinking of ways to get money with which to gamble) 5. Often gambles when feeling distressed (e.g., helpless, guilty, anxious, depressed) 6. After losing money gambling, often returns another day to get even ("chasing" one's losses) 7. Lies to conceal the extent of involvement with gambling 8. Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling 9. Relies on others to provide money to relieve desperate financial situations caused by gambling
B. The gambling behavior is not better explained by a manic episode

(as in an opioid analgesic), they are discounted from the criteria. The severity of a SUD or gambling disorder is specified by the number of criteria that are present. The presence of 2–3 symptoms is specified as mild, 4–5 symptoms as moderate, and 6 or more symptoms as severe. Once criteria for a SUD or gambling disorder are met, early remission may be specified when no symptoms are present for at least 3 months, and sustained remission may be specified when no symptoms are met for 12 months [1].

Treatment

Substance-related and gambling disorders are complex conditions that are influenced by and impact multiple dimensions of an individual's life. Treatment plans are predicated on both a specific and accurate diagnosis of the disorder, as well as a multidimensional assessment of the person who is suffering from the disorder [25]. The purpose of a multidimensional assessment is to ensure that treatment is tailored to the needs of the specific individual, addressing not just drug use, but the other biomedical and psychosocial health problems that they face (Table 14.4).

To be effective, treatment must be integrated with interventions that address medical conditions, mental health, environmental factors, family dynamics, occupational challenges, and legal problems. Treatment duration and intensity must be tailored to the patient's evolving recovery status and relapse risk, rather than predetermined or fixed doses. Evidence-based interventions are prioritized, including psychotherapies and/or indicated medication treatments. Care plans must be modified over time and reflect that these disorders are chronic relapsing conditions, for which extended monitoring and support are essential to achieving sustained remission and recovery [26].

Table 14.4 illustrates the American Society of Addiction Medicine's (ASAM) multidimensional assessment framework, which may be used to make informed decisions about appropriate levels of care, wherein specific psychosocial and biomedical treatment interventions can be offered consistent with the standard of care for the patient's health conditions [26].

Table 14.4 ASAM multidimensional assessment framework

Dimension	Description	Focus of assessment
Dimension 1	Acute intoxication and/or withdrawal potential	Past and current experiences of substance use and withdrawal
Dimension 2	Biomedical conditions and complications	Health history and current physical conditions
Dimension 3	Emotional, behavioral, or cognitive conditions	Psychiatric conditions, psychological strengths and vulnerabilities
Dimension 4	Readiness to change	Insight, readiness, and interest in changing
Dimension 5	Relapse, continued use, or continued problem potential	Predisposing, perpetuating, precipitating triggers to problem substance use
Dimension 6	Recovery/living environment	Living situation, and the surrounding people, places, and things

The multidimensional assessment integrates a patient's needs, obstacles, and vulnerabilities, as well as their strengths, assets, resources, and support structure. This information is then used to determine the appropriate level of care across a continuum, from early interventions to increasing levels of outpatient support, to residential and finally inpatient treatment options (Fig. 14.29) [21].

Treatment of Substance Intoxication and Withdrawal

Intoxication

Intoxication syndromes are generally self-limited. As the substance is eliminated from the body, the syndrome

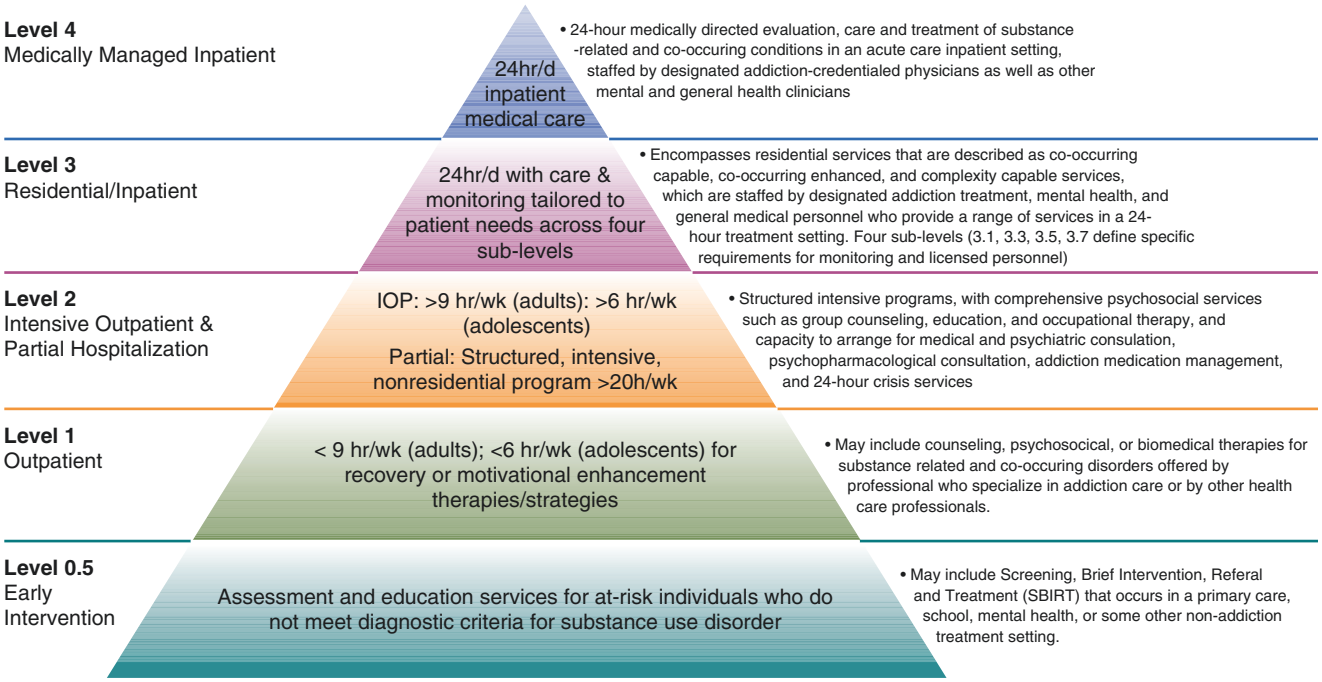


Fig. 14.29 American Society of Addiction Medicine (ASAM) levels of care for treatment

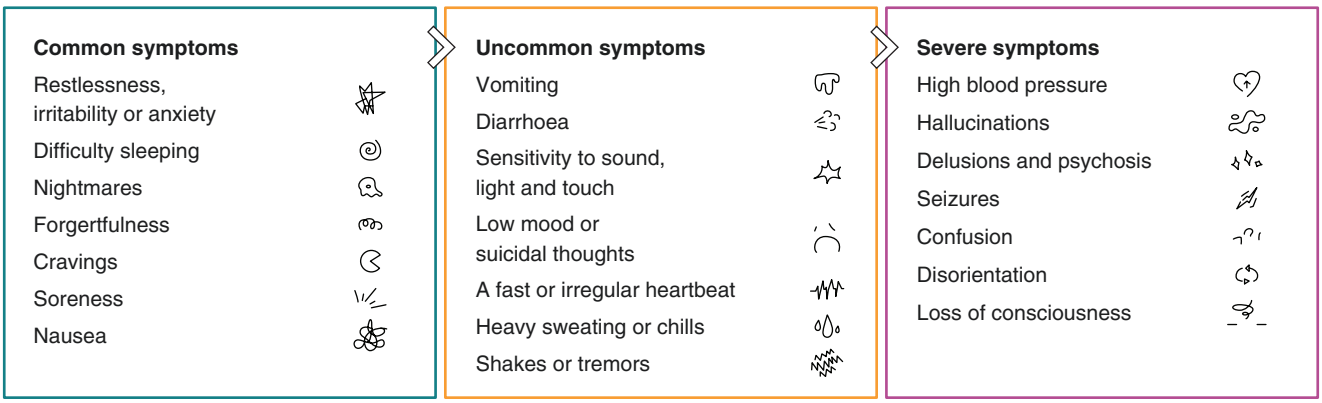


Fig. 14.30 Alcohol and other substance withdrawal symptoms

resolves. Thus, medical management of intoxication involves providing supportive measures to ensure safety (monitoring, hydration, nutrition, safe environment, support, and reassurance) and targeted interventions when the symptoms of intoxication pose a behavioral or physiological threat [12]. In the case of severe impairments or an acute overdose that is life threatening, treatment generally follows one of three approaches: increasing drug clearance, blocking the neuronal site at which the drug acts (e.g., naloxone for opioid intoxication), and pharmacologically counteracting drug effects with symptomatic management [12].

Withdrawal

While mild withdrawal syndromes may not require medical management, moderate to severe withdrawal syndromes are a major source of morbidity, and alcohol withdrawal is potentially fatal. Figure 14.30 summarizes various withdrawal symptoms people experience. The more severe symptoms occur primarily with alcohol and benzodiazepine withdrawals.

Pharmacologic treatment of any drug withdrawal syndrome generally follows one of the two approaches: suppression by a cross-tolerant medication from the same pharmacologic class—usually a longer-acting one to provide a milder, controlled withdrawal (i.e., methadone or buprenorphine for opioid medically supervised withdrawal)—and/or reducing the signs and symptoms of withdrawal by targeting the neurochemical or receptor systems that mediate withdrawal (i.e., clonidine, an alpha 2 agonist, to treat opioid withdrawal syndrome). Withdrawal treatment may be done

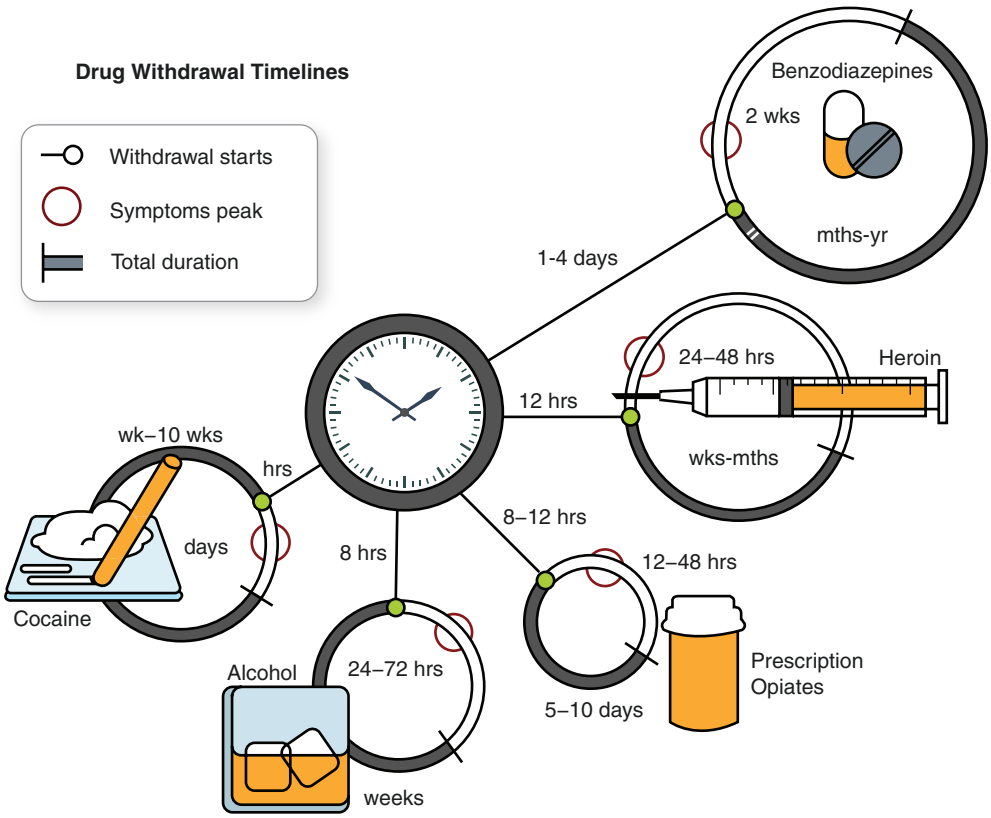


Fig. 14.31 Drug withdrawal timelines, including time to withdrawal from the cessation of substance, peak severity of symptoms, and total average duration. Withdrawal management can occur anywhere on the ASAM levels of care, from level 1 to level 4, depending on the severity and complexity of the withdrawal picture

on an outpatient or inpatient basis, depending on the withdrawal timeline of a substance (Fig. 14.31) and the severity of symptoms [12, 27].

Successful treatment of acute intoxication, overdose, or withdrawal can facilitate entry into substance use treatment by reducing uncomfortable withdrawal symptoms that negatively reinforce substance use. Even when successful, these early stages of treatment often are followed by relapse to substance use, with patients potentially reentering a "revolving door" of repeated detoxification programs. Short-term treatment of acute intoxication or withdrawal does not obviate the need for long-term treatment of substance-related disorders. Relapse rates for substance-related and addictive disorders are comparable to other medical illnesses, encouraging the utilization of a chronic disease model to implement multimodal interventions (Fig. 14.32).

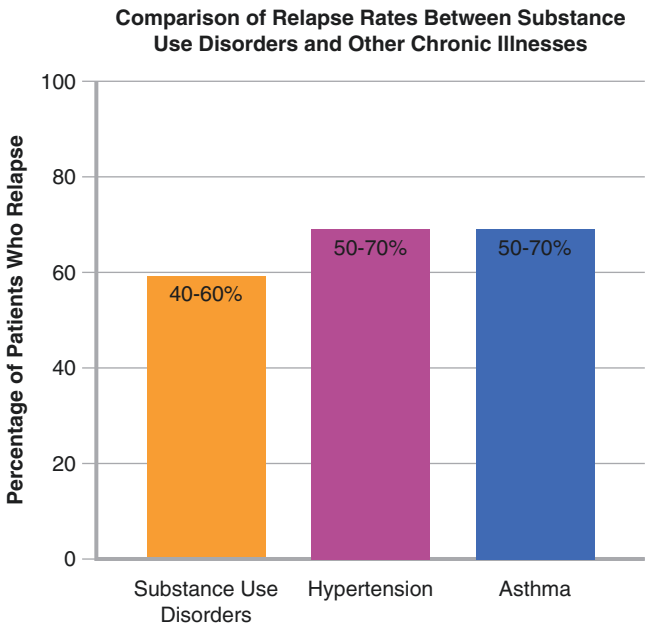


Fig. 14.32 Relapse rates for people treated for substance-use disorder as compared with relapse rates for people treated for hypertension and asthma

Treatment to Promote Relapse Prevention, Remission, and Recovery

As shown in Fig. 14.33, prolonged abstinence from substance use (and gambling) can lead to improvements in neural circuitry, with returns to levels of dopamine transporters and other markers closer to control subject comparisons

without a history of substance use. Thus, utilizing pharmacotherapy and nonmedication interventions is important to maximize the possibility of remission and recovery [25, 28].

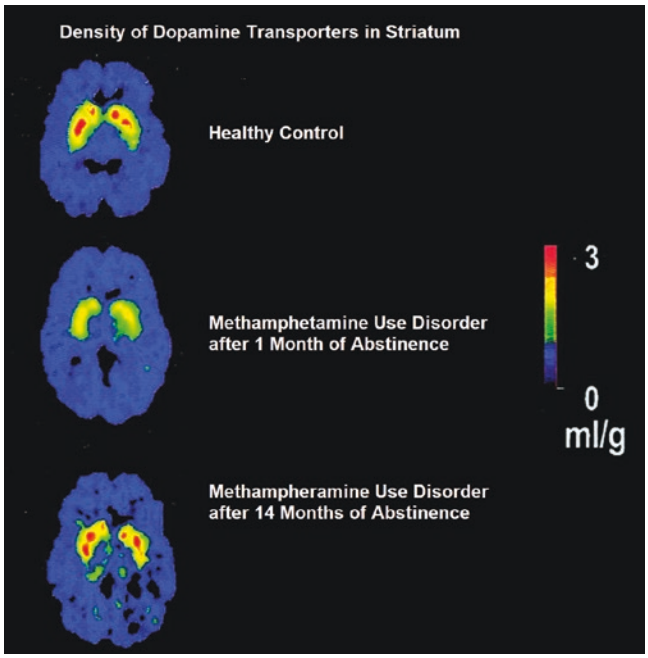


Fig. 14.33 Recovery of striatal D2 dopamine receptors after prolonged substance abstinence (example of methamphetamine). (*Adapted from* Volkow et al. [28]; *with permission*)

Pharmacological Interventions

The primary aim of pharmacological interventions for SUD and gambling disorder is to prevent relapse after abstinence, remission, or recovery has been achieved. Pharmacological interventions should be delivered in conjunction with psychosocial interventions, though if a patient is willing to start an appropriate pharmacological treatment, initiation should not be predicated on participation in a psychosocial intervention [12]. A range of established and proposed mechanisms are thought to underlie the efficacy of medication treatments for SUD and gambling disorders. Substance-specific, evidenced-based, medications approved by the US Food and Drug Administration (FDA) for opioid and alcohol relapse prevention and recovery are summarized in Table 14.5 [12]. Figure 14.34 illustrates the relative receptor activity of three FDA-approved medication treatments for opioid use disorder, while Fig. 14.35 demonstrates the mechanism of action for the three medications approved for alcohol use disorder.

To date, no FDA-approved medications are available to treat marijuana, cocaine, methamphetamine, or other SUDs [12]. Similarly, there are no FDA-approved medications for gambling disorder, though opioid-receptor antagonists have the best evidence so far and may reduce gambling urges and behaviors [6]. For all substance-related and gambling disorders, pharmacotherapy to treat comorbid mental and medical conditions is encouraged to minimize additional biological contributors to the disordered behaviors [12, 29].

Table 14.5 Pharmacological treatments for substance-use disorder

Indication	Medication	Form	Dosing	Mechanism
Opioid use disorder	Methadone	Oral	20–200 mg daily	Stimulates opioid receptor, preventing withdrawal and reducing craving
	Buprenorphine	SL; depot; implant	2–16 mg sublingual every day	Partially stimulates opioid receptor, preventing withdrawal and reducing craving
	Naltrexone	Oral; depot	50 mg once daily orally; 380 mg once every 4 weeks intramuscularly	Blocks opioid receptor, reducing reinforcing effects of substance use
Alcohol use disorder	Disulfiram	Oral	250 mg once daily (range: 125–500 mg/day; maximum: 500 mg/day)	Blocks metabolism of alcohol, leading to an aversive increase in toxic metabolites
	Acamprosate	Oral	666 mg three times daily	Blocks NMDA receptor, thought to attenuate post-acute withdrawal symptoms
	Naltrexone	Oral; depot	25–50 mg once daily orally; 380 mg once every 4 weeks intramuscularly	Blocks opiate receptors involved in the rewarding effects of drinking and craving for alcohol
Tobacco use disorder	Nicotine replacement therapy	Gum; lozenge; patch; spray	Varies with formulation; gum 2–4 mg every 1–2 h; patch 7–21 mg once daily	Stimulates nicotine receptors, preventing nicotine withdrawal and reducing craving
	Bupropion	Oral	150–300 mg daily	Inhibits reuptake of dopamine and norepinephrine, thought to influence cravings
	Varenicline	Oral	1 mg twice daily	Partial nicotine receptor agonist, preventing nicotine withdrawal and reducing craving

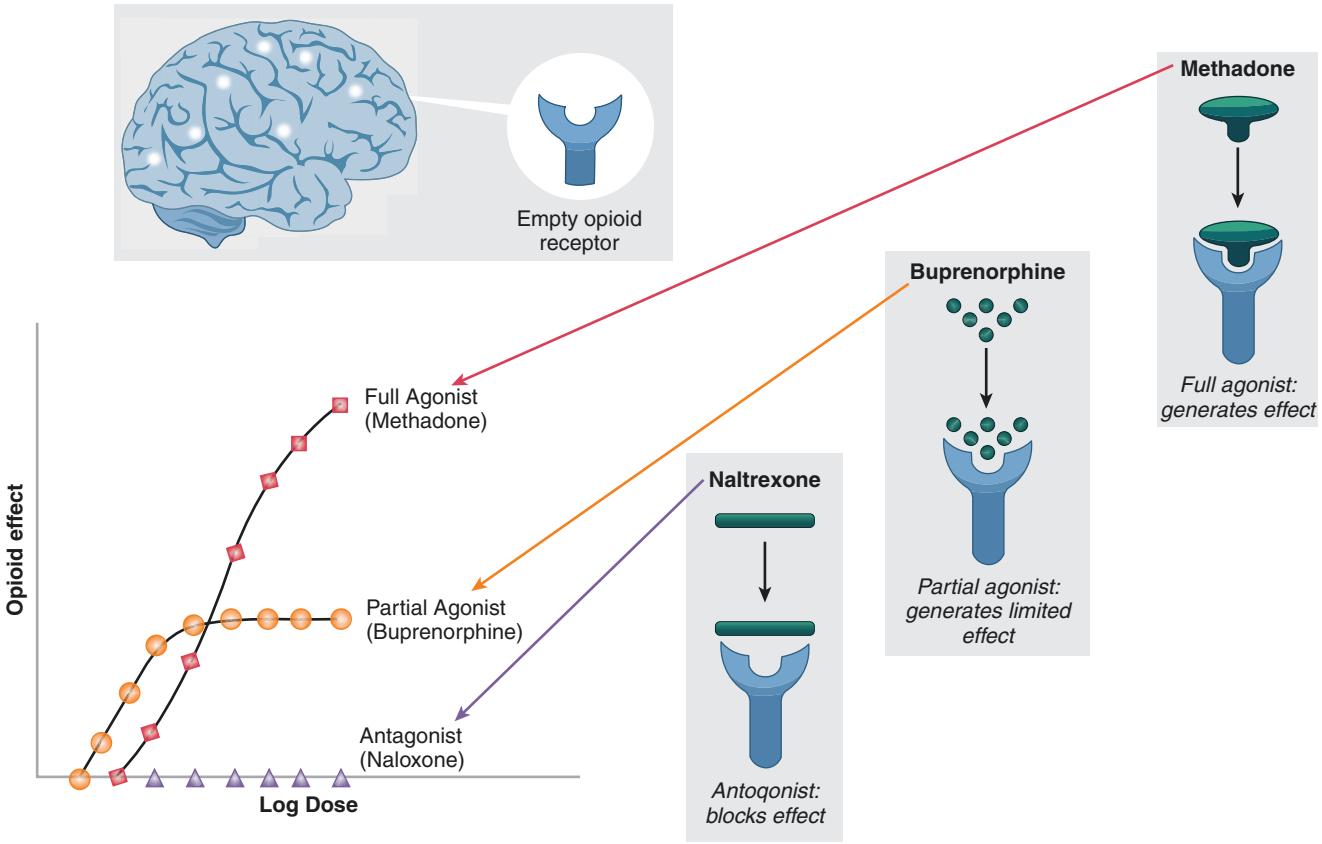


Fig. 14.34 Opioid receptor activities of naltrexone, buprenorphine, and methadone in treatment of opioid use disorder

Nonpharmacological Interventions

Whereas pharmacological interventions for SUD and gambling disorder are typically tailored, psychosocial interventions tend to have shared characteristics across the disorders. Most randomized trials of psychosocial treatment for SUDs, as well as behavioral addictions such as gambling disorder, have used manualized treatment methods to study various iterations of motivational enhancement therapy (MET), cognitive behavioral therapy (CBT), or contingency management (CM), as well as community and family interventions [6, 12, 29]. Because the underpinnings of these therapeutic models are complementary, research effort has focused as much on identifying effective combinations than on establishing the superiority of a single method.

Figure 14.36 lists psychosocial interventions focusing on the individual, their immediate support systems, and larger support communities. For gambling disorder, the best evidence exists thus far for CBT, MET, and 12-step programs, particularly when MET or 12-step programs are used in conjunction with CBT [6]. Well-supported scientific evidence shows that behavioral therapies are effective in treating substance-related and addictive disorders, but most evidence-based behavioral therapies are often implemented with limited fidelity and are underused [12, 29]. Figure 14.37 illustrates a recommended treatment algorithm for gambling disorder that integrates current evidence for pharmacologic and nonpharmacologic therapies for gambling disorder and common comorbid conditions [6].

To address the spectrum of substance-related and addictive disorders, a phase of care approach provides individuals an array of service options based on need, including prevention, early interventions, and more involved treatment to achieve sustained and recovery support [9, 22]. Figure 14.38 summarizes therapeutic objectives or interventions that are typically a focus within each phase of care. Every patient should have a tailored approach to their treatment plan based on a multidimensional assessment framework in order to

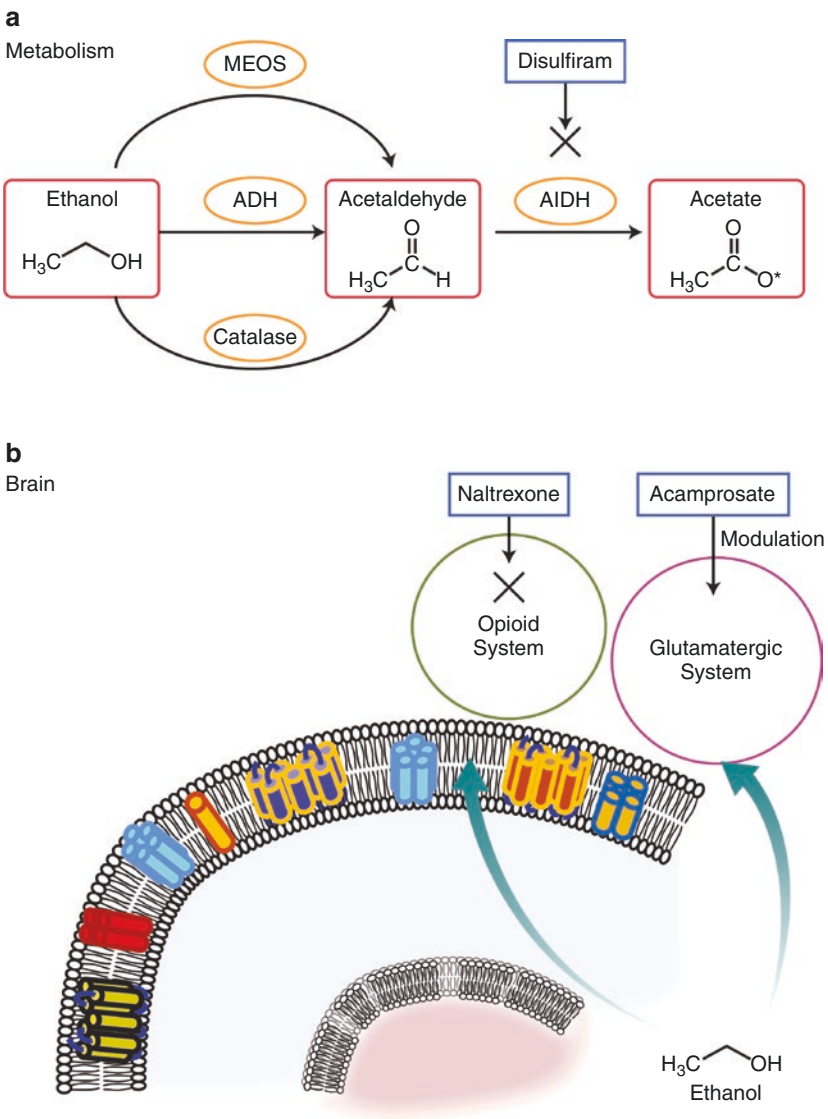


Fig. 14.35 Mechanisms of action of acamprosate (**b**-purple circle), naltrexone (**b**-green circle), and disulfiram (**a**) in the treatment of alcohol use disorder. Acamprosate inhibits aldehyde dehydrogenase (*AIDH*) leading to building up of acetaldehyde. *ADH* alcohol dehydrogenase; *MEOS* microsomal ethanol oxidizing system, and alternate first step in alcohol metabolism

integrate the unique biopsychosocial understanding of their substance use. Furthermore, the actual duration of each phase of care should be based on an assessment of clinical progress and evolving goals of care.

Over the last decade, a series of innovative care models have been developed with the objective of increasing access to evidence-based treatment services. These care models include, but are not limited to, collaborative care models to facilitate the integration of substance use treatment in primary care, telehealth services, technological applications, and consultative models.

Figure 14.39 illustrates addiction consultation teams, a model of care intended to enhance initiation of treatment for hospitalized patients with substance-use disorders. A common aim of these models is to integrate historically fragmented clinical services to create a seamless and patient-centered experience.

In conclusion, substance-related and gambling disorders are chronic diseases that have neurobiological underpinnings and are intertwined with the physical, psychological, and societal health of an individual. By utilizing a multidimensional framework to evaluate patients, a personalized assess-

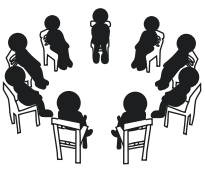
Intervention	Theory of Change
Motivational Enhancement Therapy (MET) 	Patient-centered therapy that helps individuals resolve ambivalence in order to generate commitment to change. Views readiness to change as a dynamic process involving multiple stages: pre-contemplation, contemplation, preparation, action, and maintenance, and proposes that the role of the therapist is to create the conditions that promote the patient's intrinsic motivation.
Cognitive Behavior Therapy (CBT) 	Views drug use as a learned behavior. CBT posits that by identifying the associative links and chain of events precipitating substance use, patients can identify opportunities to alter their behavioral repertoire and use alternative, healthy coping mechanisms.
Contingency Management (CM) 	Based on operant conditioning theory, posits that behaviors will increase or decrease as a function of immediate and directly associated consequences (reward or punishment, respectively). By modifying the quality and immediacy of external consequences, contingency management attempts to systematically increase the likelihood of desired behaviors and minimize undesired behaviors.
Supportive Expressive Therapy (SEP) 	Aims to cultivate a strong therapeutic alliance to enable an expressive component, in which the therapist utilizes reflective listening and interpretation to explore the patient's subjective experience, point out patterns that manifest within the therapeutic relationship, and facilitate development of self-awareness, insight, and adaptive coping.
12-Step Facilitation (TSF) 	Semi-structured therapy that encourages and systematically supports active involvement in community-based 12-step meetings, such as Gamblers Anonymous, Alcoholics Anonymous ,and Narcotics Anonymous. Sessions involve discussion of common themes from 12-step meetings, exploring patient attitudes, and overcoming obstacles.
Adolescent Community Reinforcement Approach (ACRA) 	Multi-system behavioral therapy that seeks to integrate cognitive behavioral skills training with collaborative community support, and contingency management. Utilizes a community-based approach to assist youth in promoting the structures of a healthy lifestyle.
Multidimensional Family Therapy (MDFT) 	Comprehensive systems therapy that targets the functioning of the individual within the context of his or her environment by integrating individual therapy, parent coaching, family systems therapy, and engagement of key community stakeholders, such as school, medical supports, juvenile justice, and social services.

Fig. 14.36 Selected psychosocial interventions for substance use and gambling disorders

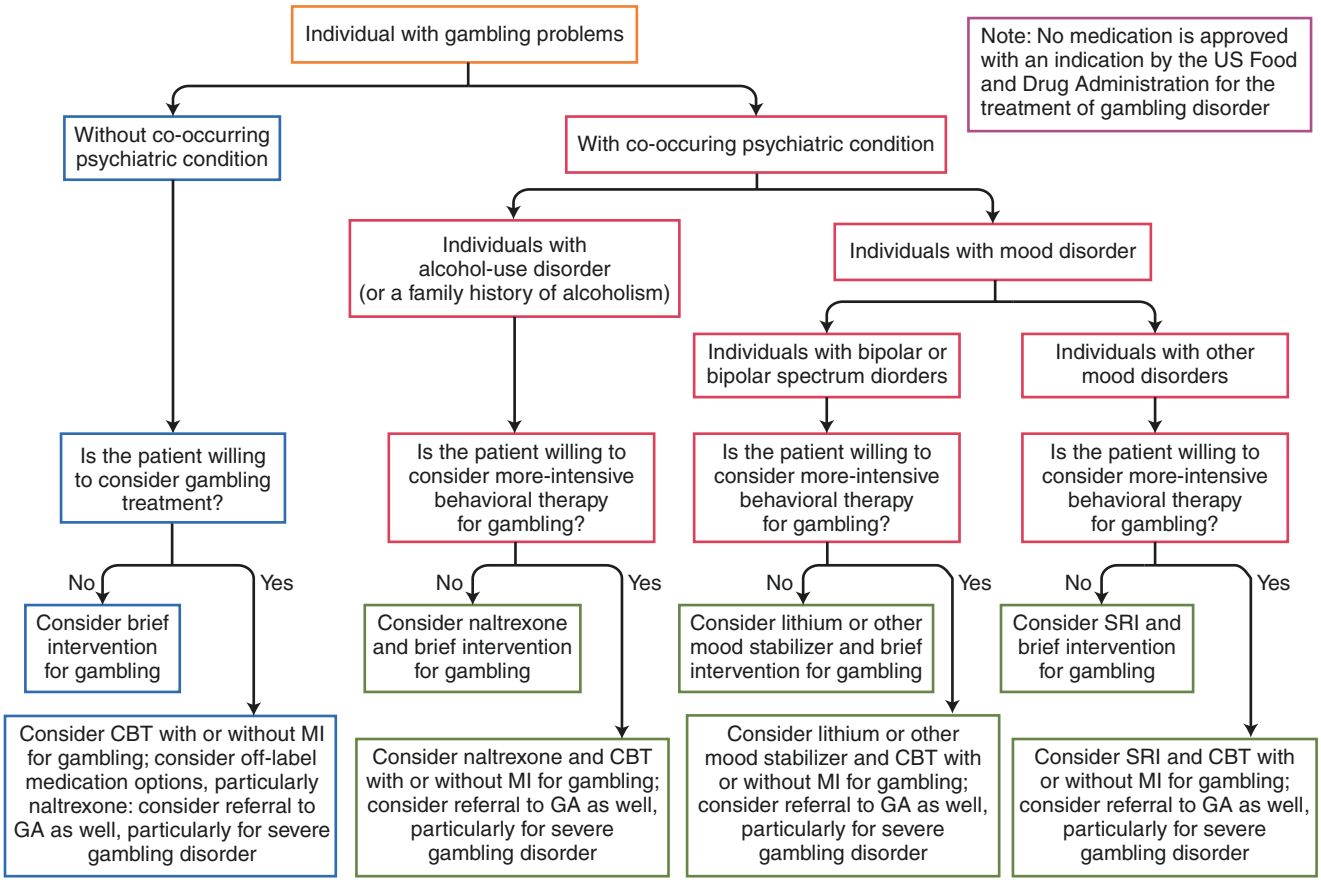


Fig. 14.37 Proposed algorithm for treatment of gambling disorder taking into account the presence of co-occurring mental health and/or substance-use disorders. (*Reproduced from* Potenza et al. [6]; *with permission*)

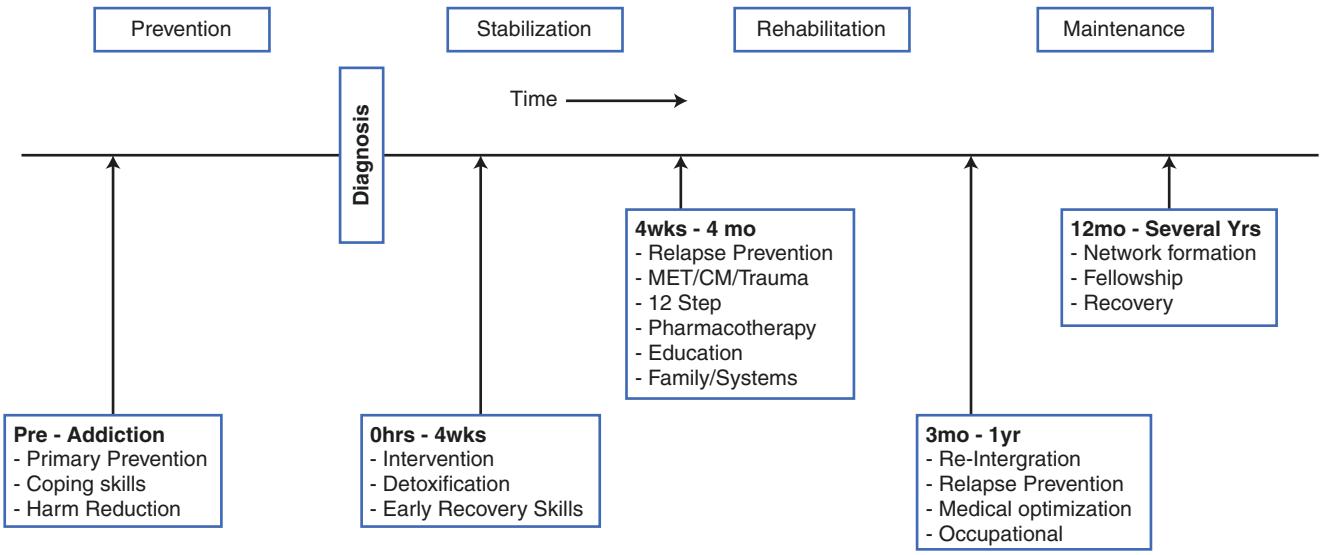


Fig. 14.38 Phases of recovery and the role of treatment interventions

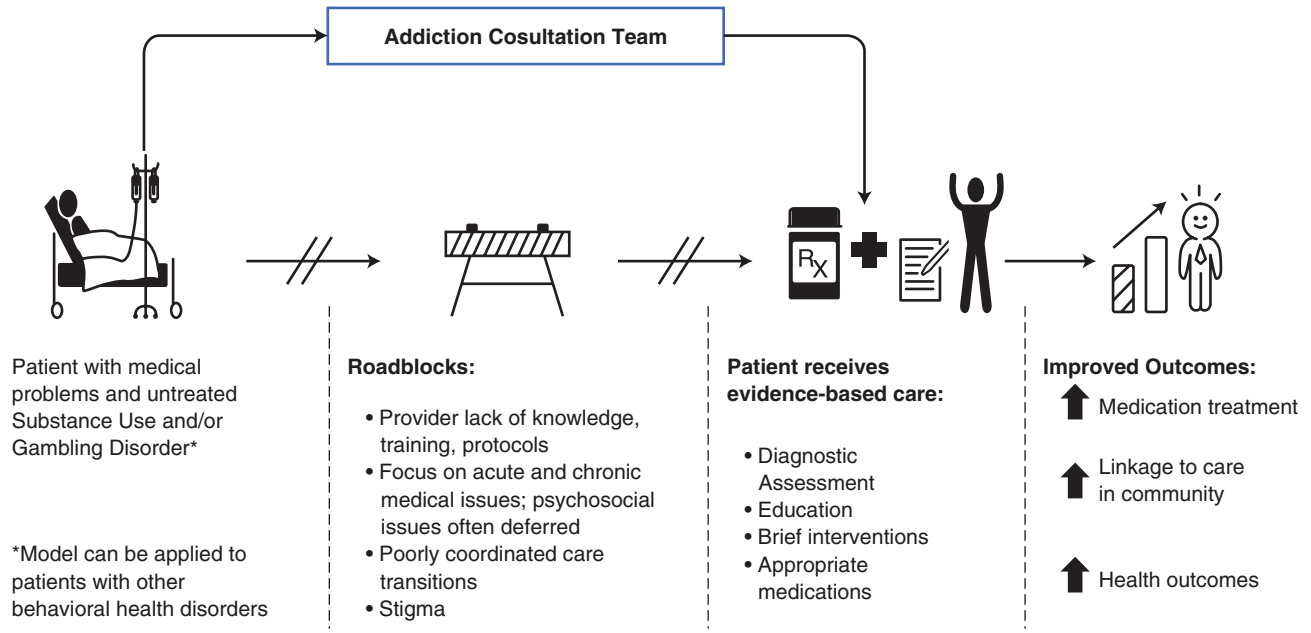


Fig. 14.39 Inpatient consultation model for treatment of substance use and gambling disorder

ment can be generated to guide a comprehensive treatment plan. With effective treatment, delivered within an appropriate continuum of care, prevention of relapse and sustainment of recovery can be achieved.

Future Directions

Additional disorders such as Internet Gaming Disorder and Caffeine Use Disorder are listed under "Conditions for Further Study" in the DSM-5 [30]. The conditions have proposed criteria similar to the other disorders listed in the Substance Related and Addictive Disorders section of the DSM-5 [30]. There was a similar discussion for inclusion of Hypersexual Disorder in the DSM-5 with criteria proposed in 2010 [31]. However, the proposed criteria were deemed to have insufficient evidence to be included in the DSM-5. The American Psychiatric Association has identified these two disorders as areas of further research.

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