Substance use disorders: a comprehensive update of classification, epidemiology, neurobiology, clinical aspects, treatment and prevention

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Substance use disorders (SUDs) are highly prevalent and exact a large toll on individuals' health, well-being, and social functioning. Long-lasting changes in brain networks involved in reward, executive function, stress reactivity, mood, and self-awareness underlie the intense drive to consume substances and the inability to control this urge in a person who suffers from addiction (moderate or severe SUD). Biological (including genetics and developmental life stages) and social (including adverse childhood experiences) determinants of health are recognized factors that contribute to vulnerability for or resilience against developing a SUD. Consequently, prevention strategies that target social risk factors can improve outcomes and, when deployed in childhood and adolescence, can decrease the risk for these disorders. SUDs are treatable, and evidence of clinically significant benefit exists for medications (in opioid, nicotine and alcohol use disorders), behavioral therapies (in all SUDs), and neuromodulation (in nicotine use disorder). Treatment of SUDs should be considered within the context of a Chronic Care Model, with the intensity of intervention adjusted to the severity of the disorder and with the concomitant treatment of comorbid psychiatric and physical conditions. Involvement of health care providers in detection and management of SUDs, including referral of severe cases to specialized care, offers sustainable models of care that can be further expanded with the use of telehealth. Despite advances in our understanding and management of SUDs, individuals with these conditions continue to be stigmatized and, in some countries, incarcerated, highlighting the need to dismantle policies that perpetuate their criminalization and instead develop policies to ensure support and access to prevention and treatment.

Key words: Substance use disorders, addiction, brain networks, social determinants of health, risk factors, prevention, treatment, chronic care model, stigma

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For most of history, persons suffering from a substance use disorder (SUD) have been viewed as individuals with a character flaw or a moral deficiency, and stigmatized with labels such as "addict" or worse. Advances in neuroscience have expanded our understanding of the brain changes responsible for this condition and have provided the basis for recognizing SUD as a progressive, chronic, relapsing disorder that is amenable to treatment and recovery.

The prevalence of SUDs is high and varies across countries and the type of drugs used (highest for tobacco and alcohol use disorders) as well as by demographic and socioeconomic characteristics of the populations. The rates of SUDs are higher for males than females and higher for younger people, with rates decreasing as both men and women age[1].

The impact of SUDs on societies as it relates to health and mortality, economics and crime is profound, and it appears to be worsening. Indeed, among all of the risk factors associated with premature death, tobacco and alcohol use rank second and seventh respectively. The high contribution to premature mortality reflects direct effects of drugs from overdoses as well as their longer-lasting negative effects on health[2].

In 2019, the number of premature deaths attributed to smoking was estimated at 7.7 million[3], to alcohol use at 2.4 million[4], and to use of other drugs at 550,700[5,6]. Unfortunately, these negative trends have accelerated in some countries. Most notable are the increases in drug-related overdose deaths in the US, which have skyrocketed over the past decade and further accelerated during the COVID pandemic[7,8]. The annual fatalities in 2021 in the US were estimated at greater than 107,000, mostly from opioids and exacerbated by the expansion of fentanyl in the illicit drug market[9], with similar trends (though not as severe) reported in Canada and the UK[10,11].

Drugs contribute to many acute and chronic diseases – including infectious, pulmonary, metabolic, cardiovascular, psychiatric and oncological diseases – and exacerbate their outcomes. The Global Burden of Disease Study, which in addition to deaths considers years lived with disability, estimated that there were 30 million years lived with disability due to SUDs in 2017[12]. Early onset, chronic or relapsing course, association with lower quality of life, and long time to remission all contribute to the large impact of SUDs.

Stigma, discrimination against individuals with SUDs, criminalization of substance use, and severely inadequate responses from health care systems in all countries, particularly in low- and middle-income countries (LMICs), further compound the adverse consequences of these conditions[13].

Significant economic costs are accrued from the production, distribution and use of illicit drugs, and those costs affect families, consumers, industries and governments[13]. For example, individuals with SUDs are less likely to be employed and more likely to experience the consequences of financial crisis[14], whereas resources devoted to drug production or distribution, law enforcement, or treatment of SUDs cannot be devoted to other goals.

Substance use and SUDs exist on a continuum of severity. In this paper, we use the term "addiction" to correspond to moderate or severe SUDs as described in the DSM-5. In the early stage of a SUD (mild SUD), the urge for drug consumption can be regulated, and we recently proposed that this could be considered as a "pre-addiction" stage that could be targeted for early prevention

interventions[15]. As the disease advances, there is a progressive loss of control over drug-taking. Individuals have an increasingly difficult time resisting the urge to use the drug, despite its adverse consequences to their health and/or social functioning – a stage that calls for therapeutic interventions.

A confluence of interacting variables that include social and biological factors and the type of drugs used determines how readily or rapidly drug experimentation transitions to mild and then severe SUD. Individual factors that influence vulnerability to SUD include genetics, exposure to adverse childhood experiences, life developmental stage at which drug exposure first occurred, personality features, and concomitant psychiatric disorders. These factors in turn are modulated by general social factors, including the amount of family and community support, social disarray and inequalities, normative behaviors regarding drugs, and drug availability and legal status, among others. The complexity of interactions between individual and social factors explains why not everyone who is exposed to drugs develops addiction, and why some individuals recover while others progress into greater chronicity and associated negative outcomes. Pharmacological differences between drugs and their availability also play an important role in addiction risk, including the time it takes to escalate from drug use into addiction.

Fortunately, effective treatment and preventive interventions for SUDs exist. A challenge for future research will be deepening our understanding of the neurobiology of SUDs, applying that knowledge to develop more effective and sustainable prevention and therapeutic interventions, and developing and scaling of services models that can reach a larger proportion of individuals with SUDs. Interventions for special populations are also badly needed.

CLASSIFICATION AND PREVALENCE

SUDs are defined as patterns of substance use that cause damage to physical or mental health[16] or lead to clinically significant functional impairment or distress[17]. They are associated with a range of physical, mental, social and legal problems[18,19]. Their clinical diagnosis is based on two main classification systems: the ICD-11 developed by the World Health Organization (WHO) and the DSM-5 produced by the American Psychiatric Association (see Tables 1 and 2).

The ICD-11 distinguishes three separate disorders[16]: a) Episode of Harmful Substance Use, defined as an episode of use that has caused clinically significant harm to a person's physical or mental health or to the health of other people; b) Harmful Pattern of Substance Use, defined as a pattern of repeated or continuous use that has caused clinically significant harm to a person's physical or mental health or to the health of other people; and c) Substance Dependence, characterized by impaired control over substance use, increasing priority of substance use over other aspects of the person's life, and persistence of use despite harm or negative consequences. The separation between Harmful Pattern of Substance Use and Substance Dependence is intended to facilitate early recognition of SUD, and to distinguish between patterns of use that may respond to brief interventions and those requiring more intensive treatment.

The DSM-5 merges the DSM-IV diagnoses of abuse and de-

Table 1 ICD-11 diagnostic requirements for disorders due to psychoactive substance use[16]

Episode of Harmful Psychoactive Substance Use

1. An episode of use of a psychoactive substance that has caused clinically significant damage to a person's physical health or mental health, or has resulted in behaviour leading to harm to the health of others.
2. Harm to health of the individual occurs due to one or more of the following: a) behaviour related to intoxication; b) direct or secondary toxic effects on body organs and systems; or c) a harmful route of administration.
3. Harm to health of others includes any form of physical harm, including trauma, or mental disorder that is directly attributable to behaviour due to substance intoxication on the part of the person to whom the diagnosis applies.
4. Harm to health is not better accounted for by another medical condition or another mental disorder, including another Disorder Due to Substance Use.

Harmful Pattern of Psychoactive Substance Use

1. A pattern of continuous, recurrent, or sporadic use of a psychoactive substance that has caused clinically significant damage to a person's physical health or mental health, or has resulted in behaviour leading to harm to the health of others.
2. Harm to health of the individual occurs due to one or more of the following: a) behaviour related to intoxication; b) direct or secondary toxic effects on body organs and systems; or c) a harmful route of administration.
3. Harm to health of others includes any form of physical harm, including trauma, or mental disorder that is directly attributable to behaviour related to substance intoxication on the part of the person to whom the diagnosis applies.
4. The pattern of use of the relevant substance is evident over a period of at least 12 months if substance use is episodic or at least 1 month if use is continuous.
5. Harm to health is not better accounted for by another medical condition or another mental disorder, including another Disorder Due to Substance Use.

Substance Dependence

1. A pattern of recurrent episodic or continuous use of a psychoactive substance with evidence of impaired regulation of use of that substance that is manifested by two or more of the following:
   a. Impaired control over substance use (i.e., onset, frequency, intensity, duration, termination, context);
   b. Increasing precedence of substance use over other aspects of life, including maintenance of health, and daily activities and responsibilities, such that substance use continues or escalates despite the occurrence of harm or negative consequences (e.g., repeated relationship disruption, occupational or scholastic consequences, negative impact on health);
   c. Physiological features indicative of neuroadaptation to the substance, including: a) tolerance to the effects of the substance or a need to use increasing amounts of the substance to achieve the same effect; b) withdrawal symptoms following cessation or reduction in use of that substance, or c) repeated use of the substance or pharmacologically similar substances to prevent or alleviate withdrawal symptoms. Physiological features are only applicable for certain substances.
2. The features of dependence are usually evident for a period of at least 12 months but the diagnosis may be made if use is continuous (daily or almost daily) for at least 3 months.

Table 2 DSM-5 diagnostic criteria for substance use disorder[17]

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. The substance is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control the substance use.
3. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.
4. Craving, or a strong desire or urge to use the substance.
5. Recurrent use of the substance resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued use of the substance despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.
7. Important social, occupational, or recreational activities are given up or reduced because of use of the substance.
8. Recurrent use of the substance in situations in which it is physically hazardous.
9. Use of the substance is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of the substance.
11. Withdrawal, as manifested by either of the following:
    a. The characteristic withdrawal syndrome for the substance.
    b. The substance (or a closely related one) is taken to relieve or avoid withdrawal symptoms.

Note: Withdrawal symptoms and signs are not established for some substances, and so this criterion does not apply.

pendence into a single category of SUD, with eleven criteria, subdivided into four groupings: impaired control, social impairment, risky use, and pharmacological criteria (i.e., tolerance and withdrawal). Three levels of severity are distinguished, based on the number of criteria met: mild (two or three), moderate (four or five), and severe (six or more)[17,20]. Differences in diagnostic criteria between the ICD and DSM contribute to some of the discrepancies in the estimated prevalence of SUDs[21].

Prevalence estimates of drug use and of SUDs are high across most countries. Alcohol is the most frequently used substance, and it is estimated that 2.3 billion people worldwide currently use alcohol (40% of adult population), with large differences across countries (from 80% to <1% of the adult population)[22]. Worldwide estimates for tobacco use indicate that, even though the rates have been decreasing since 1990, the number of people who smoke worldwide was 1.1 billion in 2019[23]. The number of people worldwide who use drugs (other than alcohol and tobacco) was estimated to be around 275 million in 2019, with the largest share among adolescents and young adults[24]. Cannabis was used by 200 million people; it was the most frequently used illicit drug and accounted for more than half of all drug law offence cases worldwide[25,26]. On the other hand, opioids accounted for the most deaths, which in the past decade have increased by 41%[25].

Among SUDs, the prevalence is highest for nicotine use disorder (estimated at 20% in past year) and alcohol use disorder (estimated at 5.1% in past year), followed by opioid use disorder and cannabis use disorder[27]. Estimates of SUD prevalence are 2.3 to 1.5 times higher for males than for females[27]. Global surveys from 2016 estimated 100.4 million cases of alcohol use disorder (70% were males), 26.8 million cases of opioid use disorder (60% were males), 22.1 million cases of cannabis use disorder (68% were males), 5.8 million cases of cocaine use disorder (68% were males), 4.9 million cases of amphetamine use disorder (65% were males), and 3.9 million cases of other drug use disorders[27]. Estimates for nicotine use disorder in 2019 were 1.1 billion and included most of the active daily smokers (36.7% of all men and 7.8% of the world's women)[28].

Countries with the highest rates of heavy alcohol drinking are Angola, Gabon, Congo and the Democratic Republic of Congo (rates >77%), followed by Russia and Papua New Guinea (60%); whereas the highest rates for drug use disorders are in the US (3.7%), Canada (2.7%), Australia (2.4%), and the UK (2.2%)[29]. Russia (32%), Indonesia (30%) and Chile (29%) have the highest rates of daily smokers as of 2012[30].

The prevalence of opioid misuse and opioid use disorder in the US has increased over the last two decades. Due to the high lethality of opioid-related overdoses (exacerbated by the expanded access to illicitly manufactured fentanyl), opioid use disorder represents one of the greatest public health challenges in the US and Canada, and is expanding into other countries. In 2021, the annual overdose mortality for opioids in the US was estimated at 81,052[31].

NEUROBIOLOGY

Drug reward and reinforcement

An evolutionarily conserved neurobiological strategy for survival is the motivation to seek out positive rewarding stimuli (e.g., food and sex) and to avoid negative aversive ones (e.g., pain and environmental threats)[32]. Dopamine is a key neurotransmitter underlying the motivation to seek positive stimuli and avoid negative stimuli[33].

Drugs tap into this basic dopaminergic mechanism both for their rewarding effects and for the neuro-adaptations that ensue with their repeated consumption. Specifically, every drug with addictive potential increases dopamine in the nucleus accumbens, through either activation/disinhibition of dopaminergic neurons in the ventral tegmental area or activation of synaptic mechanisms that lead to increased dopamine concentration at the terminals of these neurons in the nucleus accumbens[34]. Dopamine's role in drug reward and reinforcement is associated with several components, including motivation, associative learning (conditioning), incentive salience, and prediction error[35].

Different classes of drugs increase dopamine via distinct molecular targets and mechanisms (see Table 3), with resultant differences in the magnitude and the speed of dopamine increase, which in turn are factors that contribute to a drug's addictive liability[36]. In this respect, the stimulant drug methamphetamine triggers the

Table 3 Drug classes and their main mechanisms of action

Drug class	Main mechanisms of action
Alcohol	Alcohol affects multiple targets (enhances GABA, mu opioid receptor and cannabinoid signaling), indirectly increasing dopamine in the nucleus accumbens.
Nicotine	Nicotine is an agonist at nicotinic acetylcholine receptors (nAChRs). In particular its binding to the α4β2 nAChR subtype is associated with its reward-related and reinforcing effects, directly activating dopamine neurons in the ventral tegmental area (also activates modulatory neurons in this area).
Cannabinoids Cannabis, Synthetic cannabinoids	The rewarding and reinforcing properties of cannabis are due to tetrahydrocannabinol, which is a partial agonist at the CB1R receptors. Cannabidiol is neither rewarding nor addictive. Synthetic cannabinoids' agonism at CB1R also underlies their rewarding and reinforcing effects. CB1R activation modulates presynaptic release of GABA and glutamate, activating dopamine neurons in the ventral tegmental area.
Stimulants Amphetamines, Cocaine	Amphetamines, whether legally prescribed as medications for ADHD or obtained from illicit or clandestine sources (e.g., meth labs), directly release dopamine from the terminals of dopaminergic neurons via dopamine transporter (DAT) reversal and depletion of vesicular dopamine stores. Cocaine increases dopamine by inhibiting DAT, which prevents dopamine reuptake leading to its synaptic accumulation.
Opioids Morphine, Heroin, Fentanyl	Opioids' rewarding effects are due to their agonist actions at mu opioid receptors. In the ventral tegmental area, opioid binding to these receptors on GABA cells disinhibits dopaminergic neurons, increasing dopamine in nucleus accumbens, which underlies their reinforcing properties. Opioid drugs differ in potency, with fentanyl >> heroin > morphine.
Inhalants Volatile solvents, Aerosols, Gases, Nitrites	Inhalants have effects on various neurotransmitters and their receptors (NMDA↓ glycine↑, $GABA_A$↑, nACh↓, dopamine↑), enhancing dopamine release.
Sedative/Hypnotics Benzodiazepines, Barbiturates	Benzodiazepines and barbiturates, which are used as therapeutics for anxiety, insomnia, seizures, and sedation in anesthesia, are misused for their rewarding effects. They enhance $GABA_A$ receptor function, increasing dopaminergic neuron firing in the ventral tegmental area through disinhibition, which underlies their reinforcing properties.
Classic hallucinogens Psilocybin, Lysergic acid diethylamide (LSD), Mescaline, Dimethyltryptamine (DMT)	Hallucinogenic drugs act as agonists at the 5-HT2 receptor. They are predominantly used to alter mental states and do not trigger compulsive drug taking. They are the only drugs in this table not considered to be addictive. They also have effects at other serotonin receptors.
Dissociative drugs Ketamine, Phencyclidine (PCP)	NMDA receptor antagonism dissociates the cortical control and the gating of thalamus, facilitating transmission of perceptual stimuli to sensory cortices. These drugs have additional targets, including mu opioid receptors, which might underlie their increase of dopamine in nucleus accumbens.
Mixed drugs 3,4-Methylenedioxy-methamphetamine (MDMA)	MDMA is a blocker of monoamine transporters. Its effects are similar both to those of stimulants (enhancing dopamine) and of hallucinogens (enhancing serotonin).

ADHD – attention-deficit/hyperactivity disorder, NMDA – N-methyl-D-aspartate

largest dopamine increases and is associated with the highest risk for developing addiction (moderate to severe SUD) among those exposed to it (50% risk within 2 years of exposure)[37]. The contribution of the speed at which dopamine increases occur in the brain is also influenced by the route of administration[38]. This explains why drugs are more rewarding and have higher risk for resulting in addiction when they are injected or smoked, as these routes of administration result in faster drug delivery into the brain than snorting or oral consumption[39].

Additionally, the various drug types engage other neurotransmitters based on their unique pharmacological properties, and these also contribute to their rewarding and reinforcing effects. Specifically, opioid drugs and cannabis directly activate the endogenous opioid and cannabinoid systems, respectively, which by themselves are associated with hedonic effects (pleasurable sensations)[40]. Alcohol enhances GABAergic neurotransmission, which underlies its anxiolytic effects, while also indirectly stimulating endogenous opioid and cannabinoid signaling[41]. By desensitizing nicotine receptors, nicotine can inhibit negative aversive states[42]. The involvement of non-dopaminergic neurotransmitters in drug reward is made evident by studies in dopamine-deficient mice, that are still able to show conditioned place preference for cocaine or for morphine[43].

Dopamine increases in the nucleus accumbens that result from the consumption of intoxicating doses of an addictive substance are larger and longer-lasting than the increases associated with natural rewards. In the nucleus accumbens and other striatal regions, dopamine binds to high-affinity D2 and D3 receptors. When dopamine is present at high levels, as is the case during drug intoxication, it additionally binds to low-affinity D1 receptors[39]. Dopamine also binds to D4 and D5 receptors, but their relevance to the behavioral effects of addictive drugs or to reward has been much less investigated. Note that activation of D1 receptors is necessary for drug reinforcement, while activation of D2 and D3 receptors is not[44], although maximal reinforcement occurs with concomitant stimulation of D1 and D2 receptors.

The dopamine reinforcement system is dynamic, and its responses to rewards, including drugs, change as a function of the magnitude and duration of the stimulus. The first exposure to a reward (natural or drug) triggers a robust firing of dopamine neurons (phasic firing) that results in steep dopamine increases in the nucleus accumbens at levels that will bind to both D1 and D2 receptors. However, repeated exposure transforms the reward into an "expected reward", at which point dopamine neurons fire in response to stimuli that predict the delivery of the originally rewarding stimulus[45]. However, if a reward is expected but is not delivered, then dopamine neuronal firing is inhibited, signaling a "reward prediction error"[46].

The dopamine shift from reward to stimuli that predict the reward is referred to as conditioning, and drug-predictive stimuli (objects, environments, routines or emotions) are referred to as drug cues. Conditioning, driven by stimulation of D1 receptors in the nucleus accumbens, explains the addictive potential of drugs[47,48]. Once the experience from drug reward has been turned into a conditioned memory, the cues by themselves drive the desire for the drug and energize the dopamine motivational circuit that propels the behaviors to pursue it[33]. With repeated drug use, the number of stimuli that become linked (conditioned) to the drug expands, increasing the likelihood of encountering a drug-predictive cue. Once consumed, the drug's dopamine-stimulating pharmacological effects further strengthen conditioning, and this perpetuates the cycle of drug-taking[33]. This helps explain why individuals with a SUD may engage in risky, illegal or unhealthy behaviors in order to obtain the drug reward, and why return to use is so likely in people with a SUD who are abstinent.

The stimulation of D1 receptors thought to facilitate conditioning subsequently triggers neuro-adaptations in glutamatergic and other neurotransmitter systems that strengthen neuronal excitability in meso-cortico-limbic reward pathways. These neuro-adaptations are akin to those engaged in memory processes, involving changes in synaptic levels and the subunit composition of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors, and increasing the motivational value of drug-associated stimuli[33]. Parallel neuro-adaptations in other neurotransmitter systems – including GABAergic, opioid, endocannabinoid, cholinergic, serotonergic and noradrenergic ones – contribute to the disruption of mood, cognition, sleep, and stress reactivity that occurs with repeated drug use[39].

Addiction neurocircuitry

The transition from controlled drug use into addiction manifests itself in a repetitive cycle of intoxication, withdrawal and craving[49], occurring along with a deterioration of mood that the addicted individual experiences as dysphoria/depression, anxiety, irritability and anhedonia when not intoxicated[50].

The three stages of the addiction cycle emerge as a consequence of the disruption of brain networks involved with reward and motivation (reward network), executive function (executive control network), mood and stress reactivity (salience and emotion networks), and self-awareness (interoceptive and default mode networks)[51].

The length of the cycle and the prominence of each stage varies as a function of the severity of the SUD and the pharmacological characteristics of the drug(s) consumed. The principal components of the addiction neurocircuitry are different for each stage of the addiction cycle.

Reward network

The reward network involves the midbrain dopamine neurons, along with their projections to the nucleus accumbens, dorsal striatum, medial prefrontal cortex, and anterior cingulate cortex. This network is engaged during intoxication, when it is maximally stimulated, while during withdrawal it becomes hypofunctional, contributing to the decreased motivation and reduced sensitivity to non-drug rewards (anhedonia).

Dysphoria and anhedonia during the withdrawal stage, alongside exposure to drug cues, can trigger the activation of the network, which initiates the craving stage in the cycle. Craving engages the ventral prefrontal cortex and the ventral anterior cingulate cortex, sparking the drive to seek the drug that culminates in intoxication and compulsive consumption.

In the addicted state, there is a diminished sensitivity to the drug's rewarding properties, such that increasingly higher doses are needed to produce the desired effect. Over time, this leads to seeking the drug not for its pleasurable effects, but instead to escape the aversive state of withdrawal. The emergence of withdrawal symptoms upon drug discontinuation, which is particularly severe from opioids, alcohol and nicotine, contributes to perpetuating drug-taking.

The reduced sensitivity of the reward circuit in addicted individuals manifests as lack of interest in non-drug-associated activities. Brain imaging studies in humans with various SUDs have documented a decrease in striatal dopamine release (both in dorsal and ventral striatum) during the withdrawal stage, that could underlie these manifestations[49]. Clinical brain-imaging studies have also revealed decreased activation of brain regions implicated in the processing of food, sexual or monetary rewards in individuals with addiction[35]. Reactivity of striatal and prefrontal regions to punishments (referred to as negative reinforcers) is also reduced in individuals with addiction, and this reduced reactivity is associated with worse outcomes and is believed to contribute to the lack of deterrence conferred by the threats from potential negative consequences (e.g., incarceration, loss of child custody)[52] of addictive behaviors.

Assessments of the dopamine neurocircuitry in individuals with various SUDs have consistently revealed reduced striatal D2 receptors[39], and in healthy controls the levels of these receptors are inversely associated with reward sensitivity to stimulant drugs[53]. It is believed that an impaired balance between D1 and D2 receptor striatal signaling favors cue-induced reactivity while reducing behavioral control through weakened D2 receptor signaling. In hu-

mans, the enhanced sensitivity to drug cues is associated with addiction severity and worse clinical outcomes[54]. In animal models of addiction, strengthening striatal D2 receptor signaling has been found to interfere with compulsive drug-taking[55], suggesting that interventions to enhance striatal D2 receptors could be beneficial for the treatment of addiction. Few studies have been conducted to measure striatal D1 receptors in SUDs, and the results have been inconsistent[56,57].

Executive control network

The executive control network underlies various cognitive processes, including decision-making and self-regulation. Drug-induced disruptions in the function of this network contribute to the inability to avoid risky behaviors, resist drug craving, and delay gratifications.

This network includes various regions in the prefrontal cortex, whose functions are modulated by dopamine through D1 and D2 receptors in the striatum and in the prefrontal cortex itself. Repeated drug use can result in impairments that weaken self-control and promote impulsivity, in part through dopaminergic striatal effects or by direct harm to the prefrontal cortex, including the anterior cingulate cortex, orbitofrontal cortex, and dorsolateral prefrontal cortex[58]. In humans with SUD, the loss of striatal D2 receptors is associated with impaired activity of the prefrontal cortex[58,59].

Pre-existing prefrontal cortex dysfunction due to genetic factors, head trauma, or neurodevelopmental insults is recognized as a vulnerability risk factor for SUDs[60]. Interestingly, individuals at high genetic risk for alcohol use disorder (i.e., those with a family history of the disorder) but who do not suffer from alcohol use disorder themselves, have been found to have higher-than-normal striatal D2 receptor availability, which was associated with normal prefrontal cortex activity. In these high-risk individuals, the striatal D2 receptor upregulation may be protective against alcohol use disorder by strengthening prefrontal circuits involved in self-regulation[61].

The role of the prefrontal cortex appears to shift through the stages of the addiction cycle, such that the ventral and medial prefrontal cortex, including the orbitofrontal cortex and the dorsal anterior cingulate cortex (regions involved with salience attribution), are activated during the intoxication and craving stages. In contrast, the withdrawal stage is associated with a decreased activity in these medial and ventral prefrontal regions and in the dorsolateral prefrontal cortex (a region involved in decision-making)[62]. The connectivity between the prefrontal cortex and striatal regions has been consistently shown to be disrupted in individuals with SUDs[59,63,64]. Consequently, the prefrontal cortex is a target for transcranial magnetic stimulation and transcranial direct electrical stimulation interventions for the treatment of SUDs, most of which have targeted the dorsolateral prefrontal cortex specifically. The anterior cingulate cortex has also been proposed as a promising neuromodulation target for treatment of addiction[65].

Salience and emotion network

The distress and negative emotions of withdrawal are associated on the one hand with reduced dopamine signaling in response to rewards (anhedonia) and on the other with an enhanced sensitivity of the brain's stress system, including the extended amygdala, habenula and hypothalamus[66]. These neuro-adaptations in turn negatively impact components of the salience and emotion networks (including anterior cingulate cortex, amygdala and hippocampus). Sensitization of these networks likely partly underlies the frequent comorbidity of SUD with depression, anxiety and suicidality[67].

Molecular mechanisms implicated in these neuro-adaptations include upregulation of dynorphin signaling through kappa opioid receptors, which are believed to contribute to negative emotional states, although these effects appear drug-specific[68,69]. Adaptations in the hypothalamic-pituitary-adrenal axis, which regulates cortisol response during stressful circumstances, are also induced by chronic drug exposures, leading to elevations in corticotrophin releasing factor (CRF) and cortisol levels. Upregulation of CRF in the amygdala in turn plays a role in negative emotional states during drug withdrawal[51].

Interoceptive and default mode networks

Interoceptive inputs influence the shift from goal-directed, flexible behaviors toward compulsive, reflexive ones. The insula, especially its most anterior portion, is heavily involved in interoception, by integrating information about internal physiological states and conveying that information to the anterior cingulate cortex, involved with decision-making (also in front of conflicting alternatives); the ventral striatum, involved with reward; and the ventral medial prefrontal cortex, involved with salience attribution, so that they can initiate adaptive responses[70].

The two-way communication between those limbic regions and the insula suggests that the latter may play a role in the conscious awareness of internal urges. Individuals who suffered a stroke that damaged their insula were more likely to quit smoking than those who suffered a stroke in other brain regions[71], and insular activation has been associated with craving for various drugs, including nicotine, cocaine and alcohol (although not in all studies)[72]. Consequently, the insula has become a target for transcranial magnetic stimulation in addiction treatments[73].

The default mode network is involved in self-awareness and mind wandering, and its enhanced activation in the craving stage of addiction might redirect exaggerated attention toward the internal state of craving or discomfort[74]. Imaging studies have revealed impairment in brain regions within this network, including disrupted activity or connectivity involving the anterior cingulate cortex, insula, and precuneus[74].

RISK FACTORS

Several biological and social factors have been associated with

increased risk of SUDs[75], including male sex, genetics, younger age of substance use initiation, childhood adverse experiences, and psychiatric comorbidities. Drug availability and social norms around substance use are also important contributing risk factors.

Certain risk factors for SUD are more important at specific developmental stages[76], and risk factors that occur at earlier ages predispose to exposure to other risk factors later in the individual's life, often multiplying their effect. Therefore, the effect of risk factors is often not additive, but synergistic and cascading. Interventions at earlier stages of the cascade may be more likely to decrease downstream risk for SUD. Furthermore, to the extent that risk factors for SUD are shared with other psychiatric disorders, interventions on those shared factors can have spillover effects in preventing other disorders[77].

Development

Biological risk for SUDs emerges early in life, changes at various life stages, and is differentially influenced by social factors and experiences during those different life stages and transitions[78]. This developmental conceptualization of SUDs[79] helps explain the diversity of possible pathways from the various risk factors to a SUD.

Brain development during childhood and adolescence undergoes broader changes than during adulthood. In particular, the slower rate of development of the prefrontal cortex, which does not fully mature until the mid-twenties[80], places adolescents at higher risk for risky behaviors, since this region is necessary for self-regulation. This likely contributes to the increased proneness to drug experimentation during this life stage[81].

Delays in the maturation of the prefrontal cortex due to social stressors during childhood increase the risk of later drug use[82,83]. Similarly, exposure to drugs in early adolescence can perturb cortical development, including delaying the maturation of the prefrontal cortex[60]. Dysfunction of the prefrontal cortex in adolescents has been associated with a higher risk for SUDs[84].

Social environments

Epidemiological studies have repeatedly shown that environments with high levels of stressors, poor social support, easy access to drugs, and lack of opportunities and alternative reinforcers increase drug use and addiction risk[85,86]. Adverse social environmental exposures exert some influence throughout life, but effects are more pronounced when they occur in childhood or adolescence, when the brain is rapidly developing[87]. Delayed maturation of prefrontal-limbic connectivity and smaller prefrontal cortex volumes can be consequences of adverse social environments during early childhood[88].

Adverse social environments also increase the risk of drug use and SUDs across adulthood. For instance, unemployment, housing instability, and the effects of racism and discrimination may increase SUD risk and severity[89]. Overcrowding, natural or man-made disasters (conflict and war), and social factors such as low income, uncontrolled and poorly planned urbanization, and environmental degradation can also increase the risk of substance use and SUD. Primate studies that emulate social stress through hierarchical systems of dominance and subordination have shown that being an adult male of subordinate rank is associated with reduced striatal D2 receptors and is linked to higher impulsivity and drug use[90]. In humans, having poor social support systems has similarly been associated with lower striatal D2 receptors[91].

Genetics and epigenetics

Genetic factors have been estimated to account for about 50% of overall addiction risk. There are multiple gene variants that may interact to influence risk for addiction to different drugs, including genes involved in the metabolism of drugs, in dopaminergic and glutamatergic neurotransmission, in neuroplasticity, and in brain development[92]. The genetics of SUDs appears to be part of a general genetic predisposition to externalizing disorders, though common genetic predisposition has also been reported between SUDs and internalizing disorders. These common genetic vulnerabilities help explain the frequent comorbidity between SUDs and attention-deficit/hyperactivity disorder (ADHD) as well as anxiety disorders and depression[93].

Genetic studies, including genome-wide association studies (GWAS), have identified genetic variants associated with various SUDs as well as variants that appear to be protective[94]. The gene variants with the largest effects are those associated with alcohol metabolism. Variants of genes encoding for the enzymes alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), such as certain *ADH1B* and *ADH1C* alleles, result in a more rapid conversion of alcohol to acetaldehyde, the accumulation of which is aversive, and thus have a protective effect against the risk of alcoholism[95].

Gene variants can also influence the risk of misuse and addiction via a direct impact on a drug target. Examples include variants in the *OPRM1* gene, encoding for the mu opioid receptor, which has been associated with different clinical effects of opioids[96]; and variants in the *CHRNA5* gene, encoding for the alpha-5-subunit-containing nicotine receptor, which has been found to increase vulnerability to tobacco dependence[97].

Gene variants can also exert their effects indirectly, by influencing brain development, including the rate at which frontal connections mature; personality traits that may predispose to drug-seeking, such as sensation seeking; drug metabolic pathways that result in faster or slower degradation of drugs; neurotransmitters that are directly or indirectly implicated in drug reward and neuroplasticity, such as dopamine and glutamate systems; neural circuitry implicated in the addiction cycle, or cellular physiology that influences for example the side effects of drugs[98,99]. Similar to findings for other mental disorders, GWAS reveal that addiction is a polygenic disease which is influenced by multiple genes and genetic networks[100]. Currently, the ability to predict the risk of SUDs using polygenic scores is poor[101].

Preclinical studies in animal models of addiction have evaluated epigenetic modifications of gene expression and silencing in brain regions relevant to drug reward and addiction, and associated with short- and long-term effects of drugs[102]. Epigenetic modifications are believed to drive and sustain the long-lasting changes associated with addiction[103]. Among the epigenetic markers studied are histone modifications, DNA modifications, and non-coding RNAs[104], along with the expression and function of enzymes involved with reading and silencing of genes (i.e., histone acetylases, HAT; histone deacetylases, HDAC; and demethylases).

Most preclinical epigenetic studies have concentrated on regions of the midbrain dopamine reward system, including the nucleus accumbens. These studies have shown that acute and chronic drug exposures (stimulants, opioids, alcohol, nicotine) increase total cellular levels of acetylation of histones H3 and H4[105-110], apparently by unbalancing HAT and HDAC function. Moreover, the manipulation of enzymes that control histone acetylation or deacetylation or DNA methylation in the nucleus accumbens modifies drug behavioral responses, supporting their relevance to drug reward and SUDs[111,112].

The timing of substance exposure may influence the likelihood of epigenetic changes, which in turn will modify gene expression and the function of cells and circuits in the brain (and other organs). Epigenetic modifications are likely to have particularly long-lasting consequences to the brain when they occur during fetal or early infancy stages. This is because the enzymes mediating epigenetic modifications play a fundamental role in embryonic and postnatal brain development, so that their modification with *in utero* or early postnatal exposure to drugs might contribute to a higher vulnerability to addiction later in life[113].

Frequency of use is also important, as some epigenetic changes occur with short but not with repeated drug consumption, as is the case for the hyperacetylation of histone H4 along the cFos gene promoter in the striatum, whereas hyperacetylation of histone H3 at the brain-derived neurotrophic factor (BDNF) promoters is seen only after repeated cocaine exposure[114].

In parallel, studies are evaluating the effects of adverse environmental exposures, such as stress and neglect, on epigenetic modifications. These are relevant for understanding the mechanisms underlying the impact of such exposures on brain development and their enhancement of the susceptibility to addiction[113].

Human studies to assess epigenetic modifications have been limited to measures made in blood cells or in post-mortem brain[115,116]. Though there are promising results from human positron emission tomography (PET) imaging studies that measured HDAC activity in the brain of healthy people, these measures have not yet been used to study SUDs[117-119]. Clinical studies based on blood cells have found that individuals who consume drugs show epigenetic changes that appear to relate to the frequency of use in a dose-dependent manner[113]. However, drug-independent changes in addiction vulnerability triggered by adverse childhood experiences or other environmental factors might have also contributed to the epigenetic modifications reported in individuals with SUDs[120].

As the various epigenetic markers associated with drug exposures and their role in the transition to addiction or to SUD risk are better understood, they may lead to potential new medication targets. They may also help explain sex differences in drug use and addiction vulnerability, as well as changes in drug use vulnerability throughout the lifespan.

Psychiatric disorders

The presence of a psychiatric disorder – including mood, anxiety, psychotic and personality disorders, and ADHD – is associated with an increased risk for SUDs. On the other hand, SUDs are also associated with increased risk for a mental disorder. These associations are likely to reflect bidirectional links, such that having a mental disorder increases risk of maladaptive use of drugs to self-medicate, and having a SUD increases risk for developing a mental disorder, as drugs affect neurocircuits relevant to other mental disorders. Common genetic and environmental risk factors for both SUDs and mental disorders also contribute to their high degree of comorbidity[121-123].

The Epidemiological Catchment Area Study found that the overall lifetime prevalence of any SUD among those with any lifetime psychiatric disorder was almost double that for those without a psychiatric disorder (29.8% vs. 16.7%, respectively)[124]. Specifically, prevalence of SUDs in individuals with a lifetime diagnosis of bipolar disorder was 56.1% (odds ratio, OR=6.6); that in people with schizophrenia or schizophreniform disorder was 47.0% (OR=4.6); and that in persons with panic disorder was 35.8% (OR=2.9)[125]. Conversely, among individuals with a lifetime drug use disorder, 28.3% also had an anxiety disorder, 26.4% had a mood disorder, and 6.8% had schizophrenia. Analogous findings have been documented in other US large epidemiological studies, including the National Comorbidity Survey[126] and the National Epidemiologic Survey on Alcohol and Related Conditions[126,127], as well as in studies from other countries[125-128]. Comorbidity is generally associated with greater severity of illness and lower probability of remission[129].

Of particular interest is the relationship between cannabis use and psychosis. This is likely a multidirectional relationship, and its exact mechanisms continue to be a subject of debate[130]. The risk of psychosis appears to be influenced by the age of the individual at first use, the potency of the cannabis used, and how frequently it is used. A 2022 meta-analysis found an association of weekly cannabis use (vs. no use) with a 35% increase in risk of developing psychosis; it also found an association of daily or near-daily use with a 76% increase in that risk. By contrast, there was no significant increase in risk among individuals with monthly and yearly use[103].

Another area of concern with cannabis consumption is its association with a higher risk for depression and suicidality, particularly among young people. In fact, a recent meta-analysis reported an OR of 1.37 (95% CI: 1.16-1.62) for developing depression, and of 3.46 (95% CI: 1.53-7.84) for suicidal attempt, in young cannabis users when compared to non-users[131]. A higher risk of suicidal behaviors has also been reported in cannabis users with and without a

history of major depressive disorders[132] and in men with psychotic disorders who use cannabis[133].

Tobacco smoking is recognized as a major factor contributing to the lower life expectancy of persons with mental disorders[134,135]. This is especially problematic for individuals with serious mental illness, who have the highest smoking rates and higher smoking severity[136]. Although for many years psychiatrists have been reluctant to treat comorbid nicotine use disorder in psychiatric patients, because of beliefs that these patients were not interested in quitting or concerns that quitting would negatively impact their mental state[137], the evidence indicates otherwise. Specifically, many individuals with psychiatric disorders who smoke are interested in quitting[138] and respond to smoking-cessation treatments, although they might require additional support to help them quit. Moreover, there is some evidence that smoking cessation may help reduce symptoms of depression, anxiety and stress, and might improve quality of life[139]. Indeed, a recent meta-analysis concluded that there is strong evidence that mental health does not worsen as a result of quitting smoking, while there is some evidence that smoking cessation might be associated with small to moderate improvements in mental health[140].

Treatment of patients with comorbidity should include interventions for both SUD and the psychiatric disorder, because lack of treatment of one of the disorders might interfere with the success of the treatment of the other. When using medications for the treatment of SUD in a patient with a comorbid psychiatric disorder, consideration should be given to potential undesirable drug interactions. For example, whereas the use of antidepressants alongside buprenorphine in patients with opioid use disorder and depression reduced the risk of overdose[141], the use of benzodiazepines increased it, presumably reflecting synergistic respiratory depressant effects from both drugs[142].

Comorbidities between psychiatric disorders and SUDs are also relevant to prevention efforts. Specifically, because psychiatric disorders increase the vulnerability for SUDs, their early diagnosis and treatment could help prevent SUDs. Conversely, early identification of drug use in an adolescent might be an indicator of an underlying emerging psychiatric disorder, and its treatment might prevent a more severe presentation[143,144].

CLINICAL ASPECTS

Identification of SUDs

Only a minority of persons with SUDs seek treatment[145]. Since these individuals are likely to seek treatment for other conditions, such as infections or pain, screening for substance misuse in psychiatric and general medical settings is an effective way to identify SUDs[146,147].

The goal of screening is to identify substance use that increases the risk for health consequences and to develop an action plan based on severity, co-occurring psychiatric and general medical conditions, and the patient's motivation. Although SUDs are generally associated with more severe consequences than substance misuse, the latter is much more prevalent[148-150]. Thus, at the population level, most of the health consequences accrue to individuals with substance misuse rather than SUDs.

Consequently, we recently proposed the new term "pre-addiction" to identify the early stages of a SUD (mild SUD, as per DSM-5) as a focus of attention in screening for problematic drug use[15]. The term and strategy were inspired by the introduction of the term "pre-diabetes" to bring attention to the early stages of a condition amenable to intervention, in order to halt the progression to the full-blown disease. This resulted in policies in health care that now reimburse for early screening and intervention in pre-diabetes and also incentivize education of health providers in its recognition and management.

Screening and intervention for "pre-addiction" by health care providers could similarly prevent many of the adverse effects linked with unhealthy substance misuse and halt the transition into severe SUD. They could also help to cement the need for education and resources to address this early stage. There are currently screening tools that could be used for this purpose, while ongoing work is done to further validate them. However, while some interventions have been proposed for early-stage SUD (pre-addiction), this is an area that would benefit from further development of effective therapeutic tools.

Screening tools that are brief are most likely to be of practical value in health care settings where clinicians have limited time for each patient[151]. There are brief self-report instruments with high sensitivity and good specificity[146] available for use in general health settings. These are based on single questions, such as "How many times in the past year have you had five (four for women) or more drinks in a day?" for alcohol, and "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" for drugs[152,153].

A popular, evidence-based screening instrument developed and recommended by the WHO for primary care settings is the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)[154]. Eight questions about alcohol, tobacco and drug use (including injection drug use) help identify an individual's hazardous, harmful or dependent substance use. The tool can be interviewer- or self-administered. The Tobacco, Alcohol, Prescription medication, and other Substance (TAPS) is another newer and briefer (four items) valid screening tool[155].

A checklist of diagnostic criteria or, in research settings, a structured or semi-structured interview can be used to obtain a formal SUD diagnosis. Screening for substances in blood, urine or saliva can be useful to detect current use and to help monitor progress. Drug screening can also be useful if a patient cannot participate in an in-person interview[151].

SUDs as chronic disorders: onset, remission and relapse

The rate of transition from substance use to a SUD varies by the type of substance, based on its pharmacological properties[148,156,157], availability, legality, and social acceptability[156,157]. The cumulative rate of transition has been reported to be 16-67.5% for nicotine use

disorder, 14-22.7% for alcohol use disorder, 17-20.9% for cocaine use disorder, 23% for heroin use disorder, and 8.9% for cannabis use disorder[148,158]. The risk tends to be higher with younger age of initiation[158-160].

There is a growing consensus that SUDs, once developed, tend to be chronic disorders[161], reflecting long-lasting changes in brain function[50,51], that are exacerbated by the cumulative mental health and social consequences that they trigger. Although abstinence can lead to a normalization of brain structure and function over time, the level of recovery varies as a function of chronicity, type of drugs consumed, treatment and recovery support received, and intersubject variability[51]. Most individuals with a SUD alternate between periods of remission and relapse[76].

Rates of remission vary by substance, with lifetime cumulative estimates of 83.7% for nicotine, 90.6% for alcohol, 97.2% for cannabis, and 99.2% for cocaine, based on a US study[148]. Relapse rates also differ by substance: within a 3-year period, for those in remission, they are about 20% for cocaine use disorder[162] and more than 50% for alcohol use disorder[163]. About 50% of people with nicotine use disorder relapse in the first year after quitting[164]. Rates of relapse follow a hyperbolic function, with risk decreasing the longer the person remains in remission, although risk never fully disappears[164]. This is consistent with clinical experience that more intensive interventions are needed at earlier than later points in the treatment.

Long-term care of SUDs is associated with the best clinical outcomes[165]. Indeed, the Chronic Care Model, which was developed to improve the care of chronic conditions such as diabetes[166], has been proposed as a useful framework to manage SUDs[161,167]. This model emphasizes continuity of care, as opposed to episodic discontinuous care (e.g., repeated medically supervised withdrawals), with intensity of care depending on the course of the disorder. For example, an individual who recently returned to drug use may require more frequent visits or higher medication doses than somebody who has been abstinent for several years.

Examples of lifestyle management changes consistent with the Chronic Care Model involve reduction of substance use (or abstinence if possible) and use of recovery supports such as twelve-step groups. This model facilitates integration with mainstream medical practice, enhancing its reach and decreasing the costs associated with untreated SUDs[168,169].

As described in a following section of this paper, the Chronic Care Model suggests the need to develop tiered models of care. At each time point, individuals with lower need can be treated in less resource-intensive settings (community resources or primary care), while increasing severity is matched with provision of more intensive treatment approaches, such as specialized outpatient or inpatient treatment. This approach allows for the provision of the least intrusive possible care to the individual, while optimizing the use of resources at the community level.

Overdoses

A particularly dangerous complication in the course of a SUD is overdose, which, if not treated in a timely manner, can result in death. Although opioids are responsible for the most overdose deaths, there is increased recognition of the involvement of other drugs, including alcohol, and of drug combinations.

In the US, the rate of drug-related overdoses, predominantly from opioids, has risen at an almost exponential rate over the past two decades[170]. Although opioid overdose mortality was initially driven by heroin and prescription opioids, fentanyl overdoses have become progressively more important, due to their growing prevalence, difficulty of reversal, and overall lethality[171]. Treatment with naloxone – an opioid antagonist that can be administered intramuscularly, subcutaneously, intravenously or intranasally – is the most important short-term intervention to reverse overdoses. In cases in which fentanyl is involved, higher doses or repeated administrations of naloxone may be necessary. The efficacy of naloxone in reversing overdoses might be reduced when the overdose is due to combination of opioids with other respiratory depressant drugs, such as alcohol, benzodiazepines or barbiturates. Linkage with treatment services is essential to prevent repeat overdoses.

Non-lethal overdoses are much more common than lethal ones. Although their exact prevalence is not known, it is estimated that for every lethal overdose there are at least 10 non-lethal ones. Screening and monitoring of non-lethal overdoses is clinically relevant, since they frequently precede lethal ones, but unfortunately this is not routinely done. History of a non-lethal overdose should prompt an intervention either to reduce opioids in pain patients or to initiate treatment for SUD. Medications to treat opioid use disorder are the most effective prevention intervention for overdoses due to opioids[172].

TREATMENT

Treatments for SUDs include medications, neuromodulation approaches, and behavioral interventions.

Medications

Medications approved by the US Food and Drug Administration (FDA) for the treatment of SUDs are limited to tobacco (nicotine), opioid, and alcohol use disorders. Additionally, there is one FDA-approved medication for opioid overdose reversal (naloxone) and one for managing acute opioid withdrawal (lofexidine) (see Table 4). There are no approved medications to treat disordered use of stimulants, cannabis, benzodiazepines, barbiturates, inhalants, ketamine, or 3,4-methylenedioxy-methamphetamine (MDMA).

Smoking-cessation medications

Three medications for smoking cessation are approved by the FDA: bupropion, varenicline, and nicotine replacement treatments (patch, gum, lozenge, oral inhaler, and nasal spray). A mouth spray nicotine replacement treatment is also available in the UK and

Table 4 Pharmacological treatments approved for substance use disorders (SUDs) by the US Food and Drug Administration (FDA)

SUD	Indication	Medications
Tobacco (nicotine)	Smoking cessation	Nicotine replacement therapies
		Bupropion Dopamine transporter blocker
		Varenicline Partial agonist of α4β2 nicotine receptor
Opioids	Treatment of opioid use disorder	Buprenorphine Partial mu opioid receptor agonist Nociceptin receptor agonist Kappa opioid receptor antagonist
		Methadone Full mu opioid receptor agonist
		Naltrexone Mu opioid receptor antagonist Kappa opioid receptor antagonist
	Treatment of acute withdrawal	Lofexidine Alpha-adrenergic agonist
	Overdose reversal	Naloxone Mu opioid receptor antagonist
Alcohol	Treatment of alcohol use disorder	Disulfiram Aldehyde dehydrogenase inhibitor; blocks breakdown of alcohol, thereby increasing acetaldehyde levels
		Acamprosate NMDA receptor antagonist and positive allosteric modulator of GABA receptors
		Naltrexone Mu opioid and kappa opioid receptor antagonist

NMDA – N-methyl-D-aspartate

Australia. These medications lead to significantly higher rates of smoking cessation (compared to placebo) at 6 months or longer[173]. Typical treatment duration is 12 weeks, but it can be increased to 6 months or longer.

Nicotine replacement treatments work by reducing nicotine withdrawal symptoms. The various types have comparable effectiveness, with 17% quit rates at 6 months, compared to 10% for placebo[174]. The pharmacokinetics and bioavailability of nicotine from the various products differ. Patches have a slow delivery, requiring more than one hour for nicotine to peak, but result in long-lasting nicotine plasma levels for 24 hours. Nicotine reaches peak plasma concentration in 10 min when administered via nasal spray, and in 20-30 min with oral products, but plasma nicotine levels decline rapidly toward baseline within 2 hours. Supplementing the patch with a rapid-acting nicotine replacement treatment as needed, when cravings emerge, appears to improve cessation rates[175].

Electronic nicotine delivery systems (e-cigarettes) have been proposed as smoking-cessation aids[176]. A recent Cochrane review concluded with moderate certainty that they are more effective than nicotine-replacement treatments[177], but the US Preventive Services Task Force concluded that the evidence is insufficient to recommend them for smoking cessation[178]. Instead, it recommended FDA-approved medications, consistent with other US professional organizations[179,180]. This differs from the UK, where e-cigarettes are encouraged as smoking-cessation aids[181].

Bupropion is believed to reduce nicotine withdrawal symptoms by blocking the dopamine transporter (as well as the noradrenaline transporter), enhancing dopamine levels. It also has antidepressant properties via these same mechanisms, which might facilitate smoking cessation. Bupropion led to cessation rates of 19%, compared to 11% in controls[182].

Varenicline is a partial agonist at the α4β2 nicotinic acetylcholine receptor, which is implicated in nicotine's rewarding effects. This medication reduces nicotine withdrawal symptoms, while also blocking the rewarding effects of cigarettes. At 6 months, it was associated with a 26% chance of quitting, compared to 11% for placebo[183].

Cytisine, a plant-based alkaloid, is also a partial agonist of the α4β2 nicotinic receptor, and has comparable effectiveness to varenicline[184]. Though not approved by the FDA, it is prescribed for smoking cessation in Central and Eastern Europe[185].

Although medications are effective by themselves, their efficacy might be improved when combined with behavioral treatments that alter learned smoking-associated behaviors[186]. A meta-analysis of 65 randomized controlled trials (RCTs) reported 6-month cessation rates of 20% when behavioral support was added to medications, compared to 17% when medications were used by themselves[186].

Medications for opioid use disorder

Medications are the most effective interventions for preventing overdose mortality and improving outcomes in patients with opioid use disorder[187]. There are three medications used worldwide and approved by the FDA – methadone, buprenorphine and naltrexone – but there are no evidence-based guidelines to guide selection, which is most often constrained by availability[188].

Methadone is the most frequently used medication in the Middle East, Asia, South America, Africa and some European countries. It is administered daily in an oral formulation. In many countries, including the US, it has to be dispensed in licensed outpatient clinics (opioid treatment programs), which can be a barrier to care, as there are not enough licensed clinics available to serve the needs of patients with opioid use disorder in many urban and especially rural settings. When clinics are not nearby, patients must travel long distances on a daily basis[189].

Because it acts as a full mu opioid receptor agonist, methadone is indicated in patients with high tolerance, as the partial-agonist buprenorphine could trigger withdrawal symptoms in these individuals. Overall, retention is better with methadone than with buprenorphine. Higher doses (>80 mg/day) are associated with better outcomes than lower doses[190]. As a full agonist, methadone has no ceiling effect, which increases overdose risk when it is used

at doses above the patient's tolerance or when it is combined with alcohol, benzodiazepines, heroin, or other opioids. Expanding access to methadone via office-based approaches or pharmacy dispensing is a subject of interest and discussion.

Buprenorphine (a partial mu opioid receptor agonist and a kappa opioid antagonist) received FDA approval for opioid use disorder in 2002, and its use has expanded worldwide since then. It can be prescribed by clinicians in medical offices. It requires daily dosing, and typical doses range between 8 and 24 mg, with a recommended target dose of 16 mg[191]. An extended-release formulation that requires a single monthly injection was approved by the FDA in 2017 [192], and a once-a-week formulation is available in some European countries.

In patients with opioid use disorder accustomed to high doses of heroin or fentanyl or who have been maintained on high doses of methadone, buprenorphine can precipitate acute withdrawal, as it is a partial mu opioid receptor agonist[191]. Treatment of such patients might be initiated with methadone and, after a slow taper of the dose, continued with buprenorphine. Buprenorphine is less likely than methadone to depress respiration, but it can still be lethal, particularly if it is combined with other central nervous system depressants.

Naltrexone is a mu opioid and kappa opioid receptor antagonist. The effectiveness of its immediate-release formulation as a treatment for opioid use disorder has been limited by poor adherence[193], but its extended-release (3-4 weeks) formulation, XR-NTX, significantly improves treatment retention[194]. Patients with opioid use disorder must undergo supervised medical withdrawal before being inducted on naltrexone, as its mu opioid receptor antagonist properties can precipitate acute withdrawal otherwise. Although this is a barrier for some patients, current recommendations are for patients to be abstinent for one week prior to XR-NTX induction. Some protocols for faster supervised medical withdrawal (formerly known as detoxification) have been developed, but further research is needed before they can be adopted in routine clinical practice.

Another consideration when selecting a medication for opioid use disorder is whether there are any co-occurring disorders. For example, naltrexone is also effective in treating alcohol use disorder[129], whereas buprenorphine's kappa opioid receptor antagonist properties may offer benefits for individuals with comorbid depression. Methadone or buprenorphine are recommended for pregnant women, as there are insufficient data on naltrexone's safety in this population. For patients with a history of cardiac arrhythmias, methadone might be contraindicated, due to its QT-prolongation effects, which do not occur with buprenorphine or naltrexone.

Medications for alcohol use disorder

There are three medications approved by the FDA for alcohol use disorder: disulfiram, acamprosate, and naltrexone (oral and extended-release). One additional medication, nalmefene, is approved by the European Medicines Agency (EMA).

Disulfiram is an inhibitor of aldehyde dehydrogenase, which metabolizes the alcohol metabolite acetaldehyde, thereby increasing its concentration in plasma. Acetaldehyde accumulation triggers nausea, vomiting, sweating, flushing and palpitations, so that individuals treated with disulfiram stop drinking to avoid the aversive response[195]. Disulfiram reduced alcohol consumption in open-label but not in blinded RCTs, suggesting that awareness of potential negative effects improved the placebo outcomes. The efficacy of the medication is limited by poor adherence, and supervised treatment results in better success rates than non-supervised one[196]. Also, the disulfiram-ethanol interaction can be very severe; consequently, disulfiram is only recommended for the maintenance of abstinence but not as a therapy to reduce drinking[197].

Acamprosate's mechanism of action in reducing alcohol use is not fully understood. This medication is believed to modulate NMDA and GABA receptors, helping to correct the imbalance between neuronal excitation and inhibition that occurs during acute alcohol withdrawal and with protracted abstinence[198]. While RCTs of acamprosate treatment in alcohol use disorder have not always shown benefits[197], a Cochrane meta-analysis of 24 RCTs found positive effects in reducing drinking and increasing abstinence duration[199]. Acamprosate is approved by the FDA for abstinence maintenance in alcohol use disorder, and its combination with psychosocial support is associated with better outcomes[200].

Naltrexone is an antagonist of mu and kappa opioid receptors, as well as of delta opioid receptors, although with lower affinity[201]. Its blockade of mu receptors in the mesolimbic circuit is believed to reduce the rewarding effects of alcohol, decreasing its consumption[202]. Its antagonist effects at kappa receptors might be beneficial for attenuating the negative emotional state associated with alcohol withdrawal[203]. Naltrexone significantly decreases drinking days and relapse rates in patients with alcohol use disorder[204], and has been shown to reduce alcohol's rewarding effects[205,206] and number of drinks per drinking day[207]. However, its effects are modest[208], and a meta-analysis of 53 RCTs reported significant but only modest reductions in relapse to drinking[209]. Naltrexone is available as an oral and a once-a-month injectable formulation, which show similar therapeutic profiles[210]. It carries a low risk for hepatoxicity and is contraindicated for patients with acute hepatitis or liver failure.

Nalmefene, like naltrexone, is an antagonist of mu receptors that also acts as a partial agonist of kappa receptors[211]. It is approved by the EMA for the reduction of alcohol consumption in alcohol use disorder on an as-needed basis[212]. When used as needed, nalmefene decreases alcohol consumption and heavy-drinking days compared to placebo[213]. This medication might be useful in patients interested in reducing alcohol consumption but reluctant to engage in abstinence[212].

Neuromodulation

Neuronal circuits that are disrupted in addiction are potential targets for neuromodulation. Specifically, strengthening of fronto-cortical circuitry might help prevent relapse by enhancing self-control, while inhibition of the insula (mediating interoceptive awareness) might decrease craving and discomfort, thereby

facilitating remission.

Non-invasive techniques include transcranial magnetic stimulation, transcranial direct current stimulation, and low-intensity focused ultrasound[214] targeting the dorsolateral prefrontal cortex and the insula[73]. Neuromodulation of peripheral nerves via percutaneous nerve field stimulation or trigeminal nerve stimulation offers additional promising interventions in SUDs.

Invasive techniques, such as deep brain stimulation, require a surgical procedure to implant the electrodes, and are currently being studied for the treatment of severe SUDs. Case reports and small case studies targeting the nucleus accumbens for the treatment of alcohol use disorder and opioid use disorder have shown promising results[215], but much more research is needed.

At present, the only FDA-approved SUD-related indications for neuromodulation are transcranial magnetic stimulation for smoking cessation[216], and percutaneous nerve field stimulation for treatment of opioid withdrawal[215].

Behavioral interventions

Multiple behavioral therapies have been shown to be beneficial in the treatment of SUDs, by themselves or as adjuncts to pharmacotherapy. The most frequently used interventions are motivational interviewing, cognitive behavioral therapy (CBT), contingency management, and twelve-step facilitation (see Table 5).

Motivational interviewing

About 40% of people with a SUD report not being ready to stop using, highlighting the role of motivation in the treatment process[217]. Motivational interviewing has the best empirical support among approaches that convey empathy and minimize confrontation[218]. It is defined as "a collaborative conversation style for strengthening a person's own motivation and commitment to change"[219]. It helps individuals resolve ambivalence about change[220-222]. It is superior to no treatment in decreasing substance use in the short term, but its long-term effects appear less robust[221]. Another limitation is that achieving true competence in the use of the technique requires considerable training[223-225].

Cognitive behavioral therapy (CBT)

CBT is among the best-studied behavioral interventions for SUDs[226,227]. It is based on the assumption that substance use and related behaviors are learned, having been strongly associated with the rewarding properties of the substances and related cues via the reinforcement processes described earlier. CBT seeks to disrupt these learned associations by promoting awareness of behavioral patterns and teaching the patient a series of coping skills to reduce the probability of substance use, address its consequences, and intervene quickly in the case of relapse[228]. CBT helps patients to become aware of and interrupt the thought-emotion-behavior chain and to produce more adaptive coping responses[229].

The efficacy of CBT has been documented by RCTs in several SUDs[230-234]. A meta-analysis found that it had moderate significant effects when compared to minimal treatment. CBT significantly reduced consumption frequency and quantity at early, but not late, follow-up when contrasted with a non-specific therapy or treatment as usual. However, when contrasted with any specific therapy, CBT's effects were consistently non-significant across outcomes and follow-up time points[235].

Contingency management

Contingency management is based on the hypothesis that, since disordered drug use is maintained by the reward of drug intoxication and the negative reinforcement from withdrawal, emphasizing the positive outcomes associated with reduced use or abstinence may alter this balance. Because many of the positive consequences of abstinence manifest only after long periods of no use, this technique seeks to provide positive reinforcers for drug abstinence that are more immediate and predictable, such as monetary-based ones (including vouchers or goods)[236,237].

Contingency management has been successfully used to treat various SUDs[237]. It is also efficacious in reinforcing non-drug-related behavior, such as adherence to medications for human immunodeficiency virus (HIV) infection and maintaining low HIV viral load[238]. It can be used at different points of the treatment sequence, including initial engagement[167], attendance[237,239], and abstinence[237,239,240].

To effectively reinforce the target behaviors, incentives have

Table 5 Most common behavioral interventions for substance use disorders, their hypothesized mechanisms of action, and target neurocircuitry

Behavioral intervention	Mechanisms of action	Potential target network
Motivational interviewing	Strengthening motivation and commitment to change	Motivation network
Cognitive-behavioral therapy	Understand and disrupt learned associations	Executive control network
	Improve impulse control	
Contingency management	Reinforce positive consequences of drug abstinence	Reward network
Twelve-step facilitation	Peer support, role modeling and mentoring	Salience network
	Development of coping skills	

to be sufficiently large and delivered reliably and promptly[241]. Longer-duration interventions (e.g., six months or longer) are associated with better outcomes[242] Abrupt discontinuation of the intervention has been associated with relapse; gradual withdrawal schedules with lower-value reinforcers decrease this risk [229,240].

Twelve-step facilitation

Twelve-step mutual aid groups, such as Alcoholics Anonymous and Narcotics Anonymous, can help promote abstinence on their own or as part of a more comprehensive plan[243,244]. Mechanisms underpinning the efficacy of these programs[245] include peer support, role modeling of successful recovery, and sponsors' mentoring and oversight. The sense of belonging to a community of peers appears to help diminish shame, loneliness and guilt, while exposure to successes of others can inspire and instill hope. These programs also facilitate adaptive changes in social networks, increasing self-efficacy and reducing impulsivity and craving.

A recent meta-analysis[245] concluded that, for alcohol use disorder, there was high-quality evidence that manualized twelve-step interventions are as effective or even more effective than other treatments such as CBT for increasing abstinence. However, the evidence of superiority of these interventions for other SUDs is weaker[245].

Brief interventions

Brief interventions are for individuals whose substance use causes mild to moderate interference, but who do not meet criteria for a moderate or severe SUD (pre-addiction). The evidence for their efficacy is strongest for excessive alcohol use[246]. The US Preventive Services Task Force considers the evidence insufficient for other substances[247]. These interventions are generally intended for settings in which the main purpose of the visit is not substance use, such as visits to primary care or the emergency department[248].

Most brief interventions consist of feedback, advice, and goal setting to help the patient abstain from or reduce substance use or the risk of use[249]. They are generally delivered as one to four sessions that can last from 5 to 45 min[218].

Digital interventions

Digital technologies can increase access to evidence-based treatment. The digital divide remains a barrier for many underserved communities. However, for those with access to smartphones or the Internet, digital delivery can help overcome geographical and temporal barriers and can increase engagement as well as privacy[250]. It can also improve fidelity in the delivery of behavioral interventions. The results can be automatically incorporated into electronic health records, empowering individuals to be more actively involved in their own care.

Digital interventions for SUDs have demonstrated efficacy for screening and assessment[251-253], treatment[254,255] and recovery [250,256], as stand-alone tools or as adjuncts to clinician-delivered interventions. They can be equally or even more effective than clinician-delivered interventions[253]. A meta-analysis of digital interventions for cannabis use disorder found that cannabis use was significantly reduced following both prevention and treatment interventions as compared with controls. However, while the effects of prevention interventions remained significant at follow-ups of up to 12 months, effects of treatment interventions did not [257].

Perhaps the best-studied digital treatment intervention to date is the computer-based training for cognitive behavioral therapy (CBT4CBT), a six-session self-guided web-based CBT intervention for SUD[254]. CBT4CBT helps users to identify patterns of substance use and develop coping skills using video and other multimedia content. Examples of digital relapse prevention and recovery support interventions following intensive treatment include the Addiction Comprehensive Health Enhancement Support System (A-CHESS)[258] for alcohol use disorder, and the Educating and Supporting Inquisitive Youth in Recovery (ESQYIR)[259] for young people with substance abuse.

Advances in mobile and wearable sensing technologies and complex machine-learning strategies are creating new opportunities for passive identification of substance use behaviors and associated risks, potentially allowing for interventions to be delivered at moments when the patient is at high risk of return to use[260]. Future development of regulatory frameworks to evaluate the safety and efficacy of these technologies is needed.

Harm reduction

Harm-reduction interventions seek to minimize the adverse consequences of continued substance use. They include a diverse set of strategies, such as syringe services programs, access to naloxone, overdose prevention centers, and drug checking.

The distribution of sterile injecting equipment through syringe services programs is an effective intervention for preventing HIV and hepatitis C virus (HCV) infections[261]. These programs can also serve as sites for low-barrier treatment of substance abuse[262].

Naloxone, when given promptly and at adequate doses, is very effective in reversing opioid overdoses, including those from fentanyl. Wide distribution and access to naloxone in the community is one of the most effective interventions to prevent overdose deaths[263].

Overdose prevention centers provide a safe space for individuals to inject drugs under supervision. Some sites only provide supervised consumption, whereas others offer integrated services that include treatment for SUD, medical referrals, and housing, among others[264]. Mobile units ensure a more flexible deployment of services, but are limited in their capacity. Research on overdose prevention centers, while limited, has shown that they are effective in preventing overdose deaths in those who use them[264]. They also

facilitate SUD treatment engagement, and help prevent HIV and HCV infections[265].

In the US, fentanyl is the most common adulterant in heroin, counterfeit prescription pills, and stimulant drugs, and is responsible for more than half of all overdose deaths[266]. Drug checking, including through use of fentanyl test strips, allows people to test whether a drug they are planning to consume contains fentanyl or some of the common fentanyl analogues[266].

Organization of treatment services

The organization of services for delivering SUD treatments varies by countries and, within countries, by organizations responsible for SUD care. It further depends on funds, clinical infrastructure, and severity of cases treated.

The United Nations Office on Drugs and Crime (UNDOC)-WHO International Standards for the Treatment of Drug Use Disorders have set principles for the treatment system. Specifically, they recommend that treatment services should be accessible, affordable, evidence-based, diversified, and focus on improved functioning and well-being. Provision of services should be person-centered, equitable, and data-driven.

Consistent with the Chronic Care Model and with evidence that severity of disorders varies across the population and within the individual over time, it is necessary to organize service provision across a continuum of intervention intensity[151]. One way to think about this is by imaging a pyramid in which, at any given time, the lower levels require the most interventions, whereas more intensive ones (e.g., inpatient treatment) are only needed for a very low proportion of cases. Treatment systems designed with this in mind tend to be more cost-effective, because they better match need with resource utilization intensity.

Implicit in this type of model is the integration of substance use services with services for other mental disorders as well as primary care. This approach is cost-effective and person-centered and facilitates integrated care of co-occurring mental and general medical disorders in individuals with SUDs. At lower levels of need, individuals can receive informal community care through support of friends and family or self-help groups. At the next level, primary care health services can provide screening and brief interventions, referral to a specialist (when needed), and follow-up of individuals who may no longer need higher-intensity interventions. Greater need levels can benefit from outpatient or inpatient specialized treatment services. At all levels, social determinants of health and social needs should be addressed. These service models can be structured as one-stop shops, community-based networks of treatment providers, or a combination of both[151,267].

There are several models of care that have been proposed for expanding the delivery of SUD treatment in health care settings[268]. An example is the hub-and-spoke model, which has been used effectively to expand access to treatment of opioid use disorder. Services are organized around a main hub that has the expertise with use of medications for opioid use disorder; the hub is associated with treatment settings (spokes) that provide ongoing care and maintenance treatment[269].

Despite the conceptual appeal of these models, the evidence of their efficacy is still limited[270]. Furthermore, their implementation can be complicated, due to stigma and discrimination against individuals with SUDs, suboptimal allocation of resources in the treatment system, scarcity of trained personnel at different levels of the treatment services pyramid, and lack of financing or payment mechanisms for some of the interventions[271,272]. For example, if primary care physicians are insufficiently reimbursed to provide interventions for SUDs, they are unlikely to offer them to most patients that might need them.

PREVENTION

Substance use and SUDs are multidetermined, with the different risk factors playing varying roles at different life stages, from the prenatal period and childhood to early and late adulthood[78,79,164]. The goal of SUD prevention is avoiding the use of psychoactive substances, in order to foster healthy development and ensure that young people are best able to realize their potential and engage positively with their families, schools and communities[273].

Most prevention efforts have been targeted at childhood and adolescence[274], because these are periods characterized by major behavioral changes and, for adolescence, increased exposure to psychoactive substances and peer pressure[275,276]. However, risks are also present during other life stages, and there is a need to develop preventive interventions for additional age groups[146].

Preventive interventions work by mitigating risk factors (e.g., deviant behavior, drug-using peers, social neglect) and enhancing protective factors (e.g., parental support, education), and they can be implemented in family, school or health care contexts, as well as other community settings (see Table 6). Based on the risk level of the target population, they are classified as universal, selective or indicated.

Universal interventions target an entire population (e.g., an age range or a community); for example, all students in a school may be trained to improve impulse control and self-regulation. Selective preventive interventions target sub-populations at increased risk of SUDs, such as those with high-risk personality traits or living in low-resource communities. Indicated prevention, also known as early intervention, targets individuals with early signs or symptoms of substance use problems but who do not yet meet full criteria for a SUD.

The most common prevention strategy is universal school-based drug education[277,278]. The most effective programs adopt a comprehensive social-influence approach with four components: provision of information, education about the prevalence of substance use among peers, refusal skills training, and social competence or life skills. The effects of universal school-based prevention programs are generally modest[279]. Furthermore, resource limitations often preclude sustainable implementation[280].

There is also some evidence that visits in the prenatal period or during infancy to provide mothers with parenting skills[281], or offering education services to children growing up in disadvan-

Table 6 Prevention strategies for substance use disorders

Modifiable risk factor	Interventions
Impulsivity	Self-regulation training
Poor social skills	Social skills training
Exposure to stress	Stress resilience training
Insufficient parental supervision	Parenting skills training
Low self-confidence	Educational interventions; tutoring
Early substance use	Early prevention interventions
High drug availability	Supply reduction policies; community policing
Misperceptions of drug use norms	Norms training
Peer substance use	Refusal skills training
Permissive drug culture	Community-level interventions
Poverty	Jobs training; community-building interventions

taged communities[282], can help prevent substance use later in life, but additional studies are needed before these interventions can be considered evidence-based.

Communities That Care (CTC) is probably the best-known community-based approach to adolescent substance use prevention. It seeks to prevent multiple youth problem behaviors including violence, risky sexual behavior, and school dropout, in addition to substance use. CTC trains local community members on how to select which evidence-based activities to implement, based on the unique needs of the community[283]. Communities that receive CTC tend to experience reductions in risk factors for substance use and delayed initiation of delinquent behavior.

One example of a selective school-based preventive intervention is Preventure[284]. This is designed for high-risk youth with personality traits that are associated with substance use and psychopathology: hopelessness, high anxiety, high impulsivity, and sensation seeking. Preventure uses approaches based on CBT and motivational interviewing to teach young people personality-specific coping skills aimed to prevent substance use.

Parent- or family-based preventive interventions target risk factors concerning family relationships as well as peer and other social influences. They include programs focused on provision of skills to parents (e.g., communication, rule setting, monitoring), strategies for improving family dynamics, and combined student-parent interventions[285]. Parent-based interventions (i.e., focused solely on parents) and combined student- and parent-based prevention programs have been shown to produce beneficial effects on adolescent substance use outcomes[286]. Studies of primary outcomes have found that family-based programs can prevent alcohol, tobacco and drug use in young people, with effects persisting longer than 12 months. Intensive programs delivered by a trained facilitator are more consistently effective than single-session or computer-based interventions. Effective gender-specific interventions targeting mothers and daughters also exist[273].

The evidence base for substance use prevention delivered outside of school settings is limited. Yet, individuals may start using or misusing substances, such as opioids, after their school years[287]. There is still a need for research to develop and test preventive interventions for people who are at increased risk of developing SUDs, especially young adults[288]. There is also a need to study the efficacy of after-school activities (e.g., sports) and interventions targeting youth at increased risk[273]. Greater knowledge of the influence of media in the psychosocial development of young people and their risk for substance use is also needed.

Prevention interventions can also be delivered via digital media, such as videogames developed primarily for educational purposes[289]. Digital interventions have the advantage of not requiring onsite trained prevention specialists. This flexibility allows them to overcome some of the barriers to the delivery of traditional school-based programs, which require trained teachers. The portability of digital interventions also allow for their delivery in other settings, such as the home or community. Mobile health interventions, such as smartphone applications and text messaging, are commonly used to target a wide range of health behaviors in adults and represent a rapidly growing area among youth[290]. The limited existing evidence suggests that digital interventions are well accepted in this latter age group, but more systematic knowledge is needed to assess safety and efficacy[291]. There is also a need to develop quality measures for these interventions and to develop payment and reimbursement models to ensure their financial viability and stability.

In addition to existing research gaps, a common barrier is the lack of dedicated funds for preventive interventions outside research settings. Without ongoing funding, prevention interventions are difficult to implement and evaluate, leading to downstream pressure on the treatment system.

SPECIAL POPULATIONS

Opioid use disorder and pain

Chronic pain is significantly more prevalent among people with SUDs than in the general population, and this is a factor that can contribute to drug-taking[292,293]. Managing patients with co-occurring chronic pain and SUD – particularly opioid use disorder – presents unique challenges[294,295], including sometimes lack of trust between patients and clinicians regarding symptoms of pain and patterns of opioid use. Patients may fear that clinicians are unwilling to continue prescribing opioids or are going to reduce the amount prescribed. Clinicians may be concerned that patients deny or minimize aberrant patterns of opioid use or other symptoms of opioid use disorder, or that they may obtain medication through doctor shopping or from the illicit market. Moreover, it may be difficult to establish whether functional impairment or use of opioids in amounts larger than prescribed are the result of undertreated pain or represent symptoms of opioid use disorder[171,294].

Physical dependence, a neurobiological adaptation that occurs in any individual taking opioids, must be distinguished from opioid use disorder, which is a psychiatric condition with specific symptoms and diagnostic criteria[296]. Inappropriate treatment of

pain can lead to hyperalgesia, but untreated pain is a risk factor for opioid use disorder and for relapse. Since most addiction clinicians receive little training in pain management, and most pain experts receive limited training about SUDs[297], a team approach helps ensure that patients receive appropriate pain treatment while minimizing risk of opioid use disorder.

A first step in preventing opioid use disorder is limiting the use of opioids in patients not already receiving them, unless there are no alternatives for pain management[298]. However, it is important to recognize that non-opioid analgesics often yield small to moderate short-term effects on chronic pain[299], while non-pharmacological treatments for chronic pain are time-consuming and costly. Cannabinoids can provide some relief of neuropathic and cancer-related pain, but their effects are small and tend to diminish over time, and they can have significant side effects[300].

If opioids are needed to manage pain, clinicians should conduct a risk assessment that includes a comprehensive clinical history[301,302]. Modifiable risk factors, such as co-occurring disorders, should be addressed. Patients should be periodically re-evaluated to assess potential changes in their opioid treatment regimen. Clinicians should also be aware of unintended consequences of tapering opioids – including acute opioid withdrawal, uncontrolled pain, and even suicide – and balance the risks and benefits of continued opioid use[303]. If tapering is not appropriate, an alternative is to use opioids that treat both chronic pain and opioid use disorder, such as buprenorphine and methadone.

Managing acute pain in patients who are taking medications for opioid use disorder is another common clinical problem. Good communication and coordination of care are necessary to decrease the risk for undertreatment of pain. Patients on methadone should continue taking their verified daily dose, and short-acting opioids can be added for relief of acute pain[304]. Some patients may need higher dosing of opioids (up to 1.5 times higher than usual), due to increased pain sensitivity and opioid cross-tolerance, and they may require pain medications at shorter intervals.

There is no consensus yet on how to manage acute pain in patients on buprenorphine. Some proposed options include: a) adding short-acting opioids while continuing buprenorphine; b) dividing buprenorphine dosages and administering a dose every 6-8 hours, or using supplemental buprenorphine if necessary to relieve pain; c) discontinuing buprenorphine and using full-agonist opioids, then resuming buprenorphine after full-agonist opioid analgesia is no longer needed; and d) converting buprenorphine to methadone at 30-40 mg/day to prevent withdrawal and adding short-acting opioids, then resuming buprenorphine prior to discharge[304].

HIV and HCV infections

Substance use and SUDs increase the risk of HIV and HCV infections, accounting for approximately 10% of the former[305] and 38-79% of the latter[306] globally. Injection of drugs also increases risk of bacterial endocarditis, cellulitis, and abscesses and embolisms of the heart, brain and spleen, among other infections[307]. Sharing of needles and other paraphernalia increases risk. Additionally, intoxication with drugs or alcohol increases high-risk behaviors, such as engaging in unprotected sex and failing to follow preventive practices[308]. Substance use and SUDs can also negatively affect adherence to medications for HIV and HCV infections[309].

Several strategies can be used to decrease risk of HIV infection among individuals with SUDs[310], including pre-exposure prophylaxis and syringe services programs for injection drug users.

Pre-exposure prophylaxis refers to the practice of taking tenofovir (a nucleotide reverse transcriptase inhibitor) daily to decrease the risk of HIV infection. Although it can reduce risk by close to 80%, this prophylaxis has had limited uptake, probably due to its cost, the need for housing stability and access to a regular prescriber, and the difficulty of adhering to a daily medication regimen[311].

Syringe services programs reduce HIV transmission by 34-58% [312]. As already noted, it is not only distribution of sterile injecting equipment that confers positive effects to these programs. They are also sites for overdose education and naloxone distribution, linkage to SUD treatment, and HIV testing[313].

Despite these strategies, the treatment of SUDs among individuals with HIV remains challenging. Integrated care strategies in which SUD treatment, HIV care and prevention, and primary care are offered in the same clinic are recognized as best practices, but have not been widely adopted[151]. Implementation research is needed to develop, test and scale up evidence-based interventions and determine optimal approaches for each population and setting.

Adolescents

Substance use in adolescence is common. Monitoring the Future, a yearly national survey of middle- and high-school students in the US, estimates that by the time adolescents finish high school, close to 60% have used alcohol and 50% have tried an illicit drug[314]. The emergence of vaping is an important and evolving new development. Vaping devices can deliver nicotine, cannabinoids or other products, and are often supplied with flavors and packaging that are appealing to youth.

Although most adolescents who use a substance do not develop a SUD, any level of use during this period is concerning, due to youth's increased vulnerability to SUDs and the potential for long-lasting brain changes. Furthermore, research suggests that many adolescent SUDs persist into adulthood, even until midlife[315].

Efficacious interventions for adolescents with substance misuse or SUD include family-based treatments, motivational interviewing, and CBT. Screening for substance use in routine clinical visits is recommended by some professional organizations[316,317], although the US Preventive Services Task Force considers that there is currently insufficient evidence to support its efficacy[318].

There is also a paucity of evidence on pharmacotherapies for SUDs among adolescents. In the US, buprenorphine-naloxone is approved by the FDA for treating opioid use disorder in individuals 16 years of age and older. To date, no other pharmacotherapies have been approved for adolescents with SUDs, although positive

findings in RCTs have been obtained for some medications, including sustained-release bupropion and the nicotine patch for smoking cessation[319], N-acetylcysteine for cocaine use disorder[320,321], and naltrexone for alcohol use disorder[322]. In general, pharmacotherapies should be reserved for adolescents with moderate or severe SUDs who have not responded to psychosocial treatments.

Older adults

Older adults are more likely than younger people to underreport their substance use[323]. Furthermore, recognizing SUDs in elderly patients can be challenging, because clinical indicators (e.g., unsteady gait, cognitive impairment, insomnia) may reflect other common physical or psychiatric problems in this population.

Most primary care physicians do not routinely screen older adults for SUDs, even in the presence of well-known risk factors such as anxiety or depressive symptoms, increased social isolation, and poor physical health[324]. Furthermore, even among individuals with known substance use, including use of tobacco or alcohol, clinicians often fail to discuss treatment options, because they often assume that older individuals will have low motivation to change.

Although diseases resulting from tobacco use remain the leading causes of premature death in older adults, alcohol and psychoactive prescription drugs, especially opioids and benzodiazepines, are substances often used in this age group that are associated with adverse consequences[325-327]. For example, older individuals taking opioids may experience constipation, fatigue, pruritus, anorexia, somnolence, mental status changes, and nausea. Sleep apnea is also a serious risk in older adults, especially in those who have respiratory difficulties or take other medications, such as benzodiazepines, with respiratory-depressant properties.

When medically supervised withdrawal is needed, it has to be tailored for older individuals, who may have had more prolonged exposure (i.e., decades of use) and may have greater difficulty ceasing use. Slower, longer tapers (e.g., over several months) should be considered to minimize rebound symptoms, withdrawal and relapse.

Women

Although SUDs remain more prevalent in men than in women, the gender gap has been narrowing[150,328-330], possibly in part due to changes in gender roles[331]. While women have traditionally initiated substance use at a later age, this difference too may be disappearing. This is particularly concerning because, for many (although not all) substances, women progress more rapidly from use to SUD[332,333]. Patterns of comorbidity also vary between men and women: men are more likely to have multiple SUDs, while women tend to have greater rates of mood, anxiety and eating disorders in addition to a SUD[330,333].

Biological factors often make the effects of substances on women more deleterious than on men. For example, women have lower concentrations of gastric alcohol dehydrogenase, the primary enzyme for alcohol metabolism, and a lower total percentage of body water, leading to higher blood alcohol levels and greater levels of intoxication after consuming equivalent amounts of alcohol as men[334]. Similarly, women who smoke have a greater risk than men of tobacco-related heart disease, lung disease, and other health problems[335].

There are also sex differences in how likely people are to seek treatment. Men are more likely than women to seek treatment for alcohol use disorder, but less likely to seek treatment for drug use disorders, even after adjusting for sociodemographic characteristics and co-occurring disorders[336]. By contrast, there is no evidence of sex differences in treatment outcomes[337]. Some studies have reported that female patients metabolize medications at lower rates, suggesting the need to consider these differences to minimize side effects[338].

Relatively little is known about treatment of pregnant women with SUDs using medications, probably in part due to the deterrent effect of the legal consequences of perinatal substance use in some countries, as well as to regulations for the participation of pregnant women in clinical trials. The standard of care for opioid use disorder in this population includes pharmacotherapy with either methadone or buprenorphine, as part of a comprehensive treatment program that provides perinatal care and behavioral interventions. Medically supervised withdrawal or use of naltrexone are not recommended during pregnancy[339].

Evidence about smoking-cessation treatment in pregnant women is also very limited. There are no published studies on the efficacy of varenicline or electronic nicotine delivery systems. Studies of nicotine replacement treatments have not shown them to be more effective than placebo[340]. Only one small study has evaluated bupropion. We are not aware of any controlled trials of medications for alcohol use disorder in pregnant women.

Sexual and gender minorities

Individuals from sexual and gender minorities often experience discrimination and face multiple health challenges, including higher rates of substance use than other people. These higher rates are due to a combination of marketing directed at this population (e.g., tobacco); the reinforcement from increased energy, sexual drive and self-esteem experienced during intoxication with stimulants and club drugs; and the temporary relief from stress due to stigma and discrimination. Furthermore, drug use increases risk of unprotected sex and HIV infection[308].

Clinicians can help these individuals by recognizing their unique risk factors and health needs, including their fear of discrimination leading them to delay care[341]. The fundamentals of psychopharmacological and psychosocial SUD treatments are the same for patients from sexual and gender minorities as for other patients. Nevertheless, consultation with or supervision by colleagues with greater experience in treating these individuals may help clinicians whose knowledge of this population is limited.

Justice-involved populations

Individuals with SUDs are more likely than other people to come into contact with the justice system[342]. Well over half of people in state prisons and jails in the US have a SUD, and drug use – including injection drug use – is very prevalent in prisons. One in every three prisoners worldwide is estimated to have used an illicit substance during incarceration. Use of contaminated needles and syringes by prisoners increases the risk of HIV infection.

In justice-involved populations, evidence-based SUD treatment is effective in reducing substance use as well as re-offending and re-incarceration, and in facilitating recovery[343-346]. These approaches lead to better outcomes than those based on criminalization and punishment of substance use, and they are cost-effective[347,348]. Thus, it is important to intervene at every possible step in the cycle of drug use and involvement with the justice system.

Although many activities related to substance use remain illegal in most countries, failures of approaches based on criminalization of SUDs have led to a growing interest in linkage of individuals with these disorders to treatment instead of punishment[349], and a movement toward dismantling policies that perpetuate criminalization. Factors that have influenced a move away from criminalization of substance use behavior include the lack of increases in substance use in jurisdictions in which this use has been decriminalized, the increased recognition of substance use as a medical problem, and the risk of violation of human rights espoused by the United Nations[350]. Nevertheless, barriers to decriminalization remain[351]. For example, the idea that drug use is a deviant behavior engaged in by undesirable elements in society and, more broadly, stigmatization and discrimination against individuals who use substances, create resistance against policies that promote decriminalization.

A wide range of alternative measures, applicable at various points along the continuum from pre-trial through trial and post-trial phases, exist. For example, individuals can be diverted from the justice system at pre-arrest and linked to clinical and social services, including harm reduction or case management. Individuals can also be referred to the treatment system through drug courts[352].

Drugs courts are based on the recognition that charges and traditional punishments for drug possession seldom change addictive behaviors and often lead to relapse after release and new arrests. Drug courts emphasize rehabilitation, with the judge being considered part of the treatment team[353]. Having contact with the judge and random drug testing appear to be two of the most effective interventions of drug courts, while continued supervision after drug-court participation may be the most effective measure to prolong abstinence and prevent criminal activity.

The optimal approach for justice-involved individuals with SUDs should depend on the severity of their disorder and any comorbidities. According to the United Nations Standard Minimum Rules for Non-Custodial Measures[354], imprisonment should always be the last resort. The special circumstances of justice-involved women should also be considered[355].

Individuals in contact with the justice system should be systematically screened and assessed, following the procedures described above, to facilitate entry into the treatment system at the appropriate level. Linkage to services could occur during contacts with law-enforcement officers, first detention or court hearings, jails, courts, criminal justice system re-entry, and community correctional programs including probation and parole.

As a general rule, the care provided to individuals in the justice system should meet the same standards as health services in the community, based on the principle of equity. Thus, diagnostic assessment should include all the individual's medical, mental health, or social problems, as well as any factors affecting the individual's risk for reoffending or recidivism. However, resource constraints, societal attitudes, or other factors can interfere with this approach.

The vast majority of incarcerated persons eventually return to the community. However, most prisoners with SUDs do not receive treatment during their incarceration and, when released from correctional settings, they face numerous challenges in connecting with community-based treatment, social services, housing, and other essential supports[356]. This makes community re-entry a high-risk period for substance use relapse and also for overdosing. Consequently, improved connections between the justice and health care systems are essential for providing effective SUD screening, treatment, and discharge planning, including referral to services, for this population.

CONCLUSIONS

SUDs are recognized as chronic disorders that have different presentations and outcomes and frequently co-occur with other psychiatric and physical disorders. Prevention interventions, particularly if deployed in childhood and adolescence, decrease the risk for SUDs and can also reduce risk for other mental illness. Treatment interventions should be tailored to the severity of the SUD and the presence of comorbid conditions, and they should be delivered within the context of a Chronic Care Model, with the intensity of intervention adjusted on the basis of time in treatment and relapse history. Changes in policies from punitive approaches, such as incarceration, to therapeutic ones are not only cost-effective but also lead to better outcomes as it relates to drug-taking and mortality.

In the meantime, research is needed to generate knowledge with which to develop more effective prevention and therapeutic interventions that are personalized to the characteristics of the individual but also sustainable. This broad perspective can be conceptualized into five distinct domains:

a) *Basic research on the interactions between genetics, adverse childhood exposures and other social experiences (including social determinants of health), and brain development*. Large comprehensive longitudinal data sets, such as the Adolescent Brain Cognitive Development (ABCD) study[357] and the recently launched HEALthy Brain and Child Development (HBCD) study[358], are starting to generate the data needed to build such

knowledge. Similarly, analyses of large genetic databases linked with epigenetic information could help uncover the mechanisms underlying risk and resilience to drug use and SUDs. Research that identifies new molecular or circuit-based targets for treatment is also needed, as is research that links epidemiological findings to their underlying neurobiological substrates.

b) *Epidemiological research, including wastewater epidemiology, coupled to electronic health records and medical surveillance systems*. Such research could help provide more timely metrics of the nature and type of drug problems, which is essential to better tailor interventions, allocate resources, and monitor outcomes. Epidemiological research can also help generate hypotheses about the causes of SUDs and identify targets for prevention and treatment. It can provide information to test or simulate the effects of policies and to estimate the effects of interventions when they cannot be tested using randomized designs.

c) *Therapeutic development*. Translational research to expand the medications available to help treat SUDs, as well as research on various central and peripheral neuromodulation interventions (including studies to determine which brain areas to stimulate, optimal frequency and duration of stimulation, and the value of these interventions as adjuncts to improving retention in treatment when combined with medications), is another opportunity area. Importantly, research on alternative outcomes for medications for SUDs other than abstinence – such as improvements in sleep, depression, anxiety and craving – will expand the pipeline of treatments that can benefit patients even when they do not result in abstinence. The expansion of telehealth and other digital technologies (as well as hybrid models) needs to be accompanied by a better understanding of how to optimize their use and for whom. Similarly, further research on the use of virtual technologies for treatment of SUDs is needed. Finally, development of biomarkers that can help guide treatment selection beyond the information provided by clinical variables would help advance personalized care in SUDs.

d) *Research on implementation, services and economics of substance use treatment and prevention*. This research is needed to help develop optimal evidence-based care models that are effective, equitable and sustainable, and can be adapted to the needs and preferences of various communities.

e) *Policy research*. Understanding the consequences to the community and individuals, including those from marginalized groups, of policies pertaining to drug legalization, decriminalization, treatment reimbursement, and regulation of scheduled drugs will provide guidance on strategies to minimize risk for populations and to prevent stigmatization and discrimination against individuals who use drugs, to ensure equity across groups.

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