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Review

Advances in the study of pharmacotherapy for addiction to naturally-derived psychoactive substances

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ABSTRACT

Drug addiction, a disorder characterized by chronic relapse and compulsive drug use, poses a significant threat to public safety and human health. Addictive substances can be categorized as natural, semi-synthetic, or synthetic based on their origin. Additionally, they can be classified into three groups according to their pharmacological targets: opioids, hallucinogens, and cannabinoids that act on G-protein-coupled receptors (GPCRs); alcohols, nicotine, ketamine, barbiturates, and benzodiazepines (BDZs) that affect ligand-gated ion channel-type receptors; and psychostimulants that interact with monoamine transporters. Current treatments for drug addiction primarily include substitution therapy and non-pharmacological approaches. However, these methods have limitations, particularly in addressing the underlying causes of relapse. Several drugs in clinical trials have demonstrated potential therapeutic effects for addiction to opioids, heroin, cocaine, and other substances. This review examines the origins and pharmacological mechanisms of addiction to naturally-derived psychoactive substances (NPS) and provides an overview of recent advancements in pharmacotherapy for drug addiction.

1. Introduction

Humans have cultivated papaver somniferum and extracted opium from its fruit for millennia. A series of semi-synthetic and synthetic opioids emerged in the 19th Century. Paul Janssen synthesized fentanyl in 1960, which was introduced in the United States in the 1970s under the trademark Sublimaze®. As an intravenous anesthetic, fentanyl offers advantages such as a shorter onset of action and enhanced potency (approximately 50–100 times that of morphine), making it the most widely used synthetic opioid in surgical and clinical settings [1]. However, fentanyl's increasing popularity led to its misuse. In the 1980s, deliberate abuse of drugs, including fentanyl, dulcolax, and sufentanil, emerged, particularly among professionals such as anesthesiologists and surgeons [2]. This contributed to the initial opioid crisis, primarily caused by overprescription of opioid analgesics. As semi-synthetic opioids developed, some individuals with addiction turned to inexpensive, readily available, high-purity heroin. By 2016, illicit synthetic opioids surpassed prescription opioids and heroin as the leading cause of opioid addiction and mortality. The opioid crisis has generally been characterized by these three distinct waves. Recent evidence suggests a fourth wave of the opioid crisis, marked by increased fatalities resulting from the concurrent use of psychostimulant drugs (predominantly methamphetamine) and opioids [3].

"What is addiction and how does it work ?" remains one of the 125 major cutting-edge scientific questions facing the international scientific community, as identified by Science [4]. Certain natural substances under development have demonstrated addictive properties and abuse risks, potentially causing harm to individuals and society. Consequently, their use has been restricted, necessitating strict dosage control and regulation to mitigate addictive properties and potential harm. The evolution of addictive drugs has progressed from natural to semi-synthetic and synthetic formulations. This progression has resulted in decreased drug costs, increased availability, and significantly enhanced purity and potency, rendering all drug types substantially more harmful to humans. Concurrently, the structural complexity and mechanisms of action of these compounds have intensified. Recent years have witnessed notable advancements in drug addiction research. This review summarizes the pharmacological effects of common natural sources and several representative addictive drugs, emphasizing therapeutic agents developed in recent years targeting opioid receptors, dopaminergic receptors, glutamatergic receptors, and other prominent targets. The discussion encompasses both marketed and clinical research-stage compounds, both naturally sourced and synthetic, aiming to provide insights into the prevention and treatment of drug addiction.

2. Introduction to addictive drugs

A shared characteristic of addictive substances is their tar-

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geting of the ventral tegmental area (VTA), resulting in a substantial increase in dopamine (DA) levels within the mesocorticolimbic system and initiating adaptive synaptic plasticity through diverse cellular mechanisms [5]. Based on their distinct pharmacological mechanisms, addictive substances can be categorized into three groups: (1) opioids, cannabinoids, hallucinogens, and similar drugs suppress γ-aminobutyric acid (GABA) release from VTA interneurons, indirectly enhancing DA neuron firing *via* their respective G-protein-coupled receptors (GPCRs), a process termed disinhibition; (2) nicotine, alcohol, ketamine, benzodiazepines (BDZs), and barbiturates depolarize DA neurons by interacting with ligand-gated ion channel-type receptors; and (3) psychostimulants, including cocaine and amphetamines, modulate extracellular DA levels by inhibiting or reversing monoamine transporter activity [6] (Fig. 1).

2.1. Drugs acting on the GPCRs

2.1.1. Opioids

In the early 19th Century, researchers isolated morphine and codeine, two prevalent alkaloids, from opium. This led to the development of several semi-synthetic opioids, including heroin (diacetylmorphine) and oxycodone, as well as synthetic opioids like methadone and fentanyl [7]. Opioids, a class of compounds derived from opium alkaloids and their synthetic analogs, encompass a range of sedative-hypnotics with anesthetic, analgesic, and other pharmacological properties. Prototypical opioids such as morphine and codeine have been extensively employed for their potent analgesic effects; however, their high potential for dependence and abuse has led to increasingly restricted clinical use. The pharmacological actions of opioids are mediated through four GPCRs: the μ receptor, the κ receptor, the δ receptor, and the nociceptin/orphanin peptide (NOP) receptor [8]. The μ receptor is primarily associated with euphoria and respiratory depression and is considered the main driver of drug addiction [9]. The κ receptor induces an anti-reward effect, while the δ receptor is linked to anxiety and depression levels [10]. NOP receptor activation enhances μ-opioid peptide (MOP) receptor-mediated analgesia, inhibits the release of DA, 5-hydroxytryptamine (5-HT), glutamate, GABA, and other neurotransmitters, and influences reward, mood, movement, and other central nervous system (CNS) functions [11]. Opioid receptors predominantly signal through intracellular G proteins and/or GPCR kinases (GRKs) and β-arrestins [8]. Opioids activate presynaptic terminally expressed μ receptors, inhibiting calcium channels or activating voltage-gated K^+ channels to reduce GABA release; they also activate Kir3/G protein-coupled inwardly rectifying K^+ (GIRKs) channels coupled to μ receptors on postsynaptic cytosol and dendrites, leading to supersaturation [6]. The combined effect indirectly increases DA release, thereby enhancing drug-seeking behavior [12]. μ receptors are concentrated in brain areas regulating pain and reward, and are widely distributed in regions governing emotions and breathing [13]. Long-term opioid use can result in symptoms such as confusion, blank stares, slurred speech, slowed breathing, drowsiness, and, in severe cases, death from respiratory depression. Opioid addiction often entails complications like pain sensitization and mood disorders, increasing patients' suicide risk. Intravenous abuse can also lead to various infectious comorbidities, including HIV and hepatitis C virus infections [13].

2.1.2. Marijuana

Marijuana comprises 104 cannabinoid compounds, with Δ^9-tetrahydrocannabinol (Δ^9-THC) being the primary psychoactive constituent [14]. THC acts as an agonist for cannabinoid receptors 1 and 2 (CB_1 and CB_2 receptors). The activation of CB_1 receptors contributes to cardiometabolic disorders, while CB_2 receptor activation is associated with anti-inflammatory effects on immune cells [15]. The legalization of cannabis for medical and recreational use in various countries has coincided with an increase in THC content, leading to a significant rise in reports of severe adverse cardiovascular events. Furthermore, there is an emerging trend of synthetic cannabinoid analogs for recreational use [16]. These synthetic compounds function as full agonists of CB_1 receptors, exhibiting potency hundreds of times greater than THC, a partial agonist. Consequently, they possess a higher potential for addic-

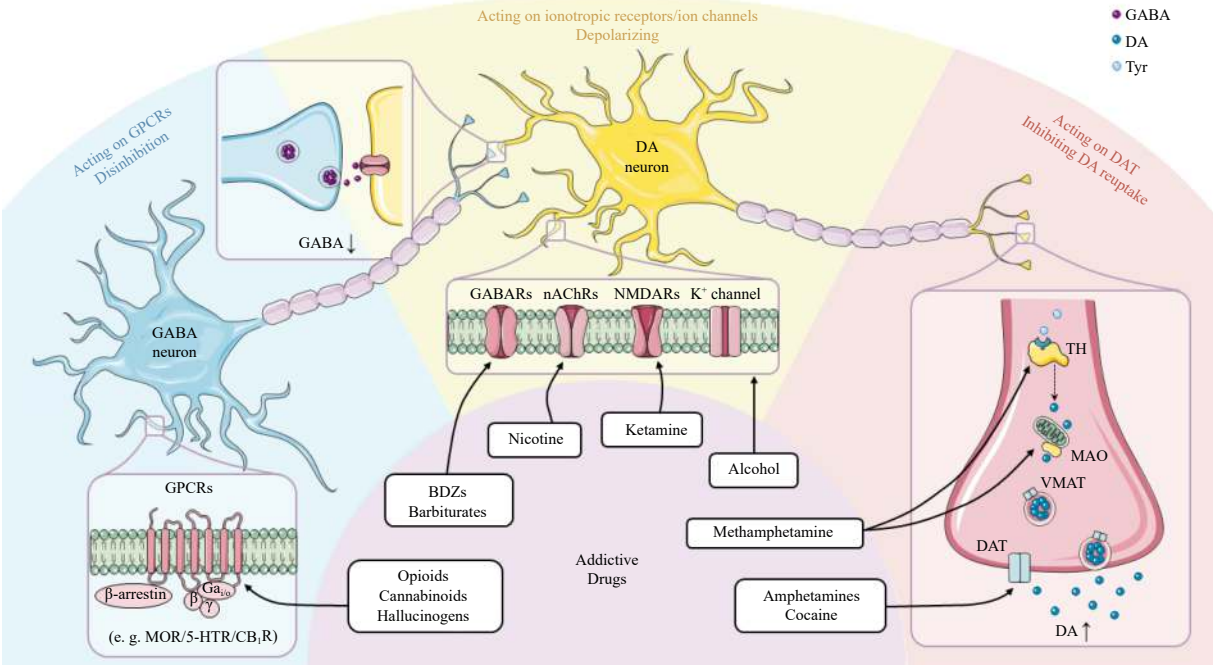

Fig. 1 Pharmacological targets of action of representative addictive drugs. GABA, γ-aminobutyric acid; DA, dopamine; Tyr, tyrosine; THC, tetrahydrocannabinol; BDZs, benzodiazepines; TH, tyrosine hydroxylase; MAO, monoamine oxidase; VMAT, vesicular monoamine transporter; DAT, dopamine transporter; GPCRs, G-protein-coupled receptors; MOR, μ-opioid receptor; 5-HTR, 5-hydroxytryptamine receptor; CB_1R, cannabinoid receptors 1; GABAR, γ-aminobutyric acid receptors; nAChRs, nicotinic acetylcholine receptors; NMDARs, *N*-methyl-D-aspartic acid receptors.

tion and adverse cardiovascular events [15]. Both smoking and intravenous administration of THC can induce symptoms including limb numbness, dizziness, hallucinations, palpitations, and concentration impairment. These effects are often accompanied by cognitive deficits such as self-consciousness disorders, psychosis, and temporal disorientation [17].

THC activates CB_1 receptors in GABAergic neurons, reducing GABA release and consequently increasing DA neuron firing. Traditionally, CB_1 receptors were thought to be primarily expressed in CNS neurons, while CB_2 receptors were believed to be predominantly found in peripheral immune cells. However, recent evidence indicates that CB_2 receptors are also expressed in neuronal and glial cells within addiction-associated brain regions, contributing to central neurological function, immune response, and neuroinflammation [18]. During addiction, inflammation, and other pathological conditions, CB_2 receptor expression in the brain is upregulated [19]. Furthermore, studies have shown that activation of CB_2 receptors in mouse VTA DA neurons decreases neuronal excitability and drug-seeking behavior [18]. Unlike CB_1 receptors, which are predominantly presynaptic, CB_2 receptors are mainly located in postsynaptic dendritic regions, and their activation reduces the firing and excitability of VTA DA neurons [20]. Additionally, THC modulates the glycine receptor (GlyR) and potentially interacts with GPR55 and 5-HT_{3A} receptors [17].

Marijuana contains numerous compounds with potential therapeutic applications, beyond its well-known constituent, THC. Cannabidiol (CBD), a monoenol compound extracted from cannabis, exhibits analgesic, anticonvulsant, anxiolytic, neuroprotective, and anti-inflammatory properties. It has been utilized in the treatment of epilepsy and other neurological disorders [21]. However, the precise mechanisms underlying CBD's anti-inflammatory and tissue-protective effects require further clinical validation to fully elucidate their therapeutic potential.

2.1.3. Serotonergic psychedelics

Hallucinogenic drugs are typically classified into two categories: "classical hallucinogens" and "dissociative anesthetics" (e.g., ketamine) [22]. Classical hallucinogens, also known as serotonergic psychedelics, include plant-derived psilocybin, semi-synthetic lysergic acid diethylamide (LSD), and other substances that primarily induce their hallucinogenic effects through the serotonin system. These compounds primarily function as agonists at 5-HT_{2A} receptors and have demonstrated activity at 5-HT_{1A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_6, and 5-HT_7 receptors [23]. Hallucinogens can be further subdivided into three structural groups: tryptamines, lysergamines, and phenylethylamines, with varying affinities for 5-HT receptor subtypes among different derivative classes [24]. While hallucinogens induce euphoria and intense hallucinations, chronic abuse may result in perceptual distortions, cognitive disorganization, emotional instability, and symptoms such as delusions and depression.

2.1.4. Kratom extracts

Kratom, derived from the leaves of *Mitragyna speciosa* Korth. (Rubiaceae), a tree indigenous to Southeast Asia, has been traditionally used to alleviate diarrhea, pain, and fatigue, as well as serve as an opium substitute [25]. The leaves can be consumed directly by chewing or processed through soaking or crushing. Highly concentrated preparations of its active components potentially pose greater risks. Mitragynine and 7-hydroxymitragynine, the primary active alkaloids in kratom, exert their pharmacological effects through various targets, including opioid receptors, 5-HT, and adrenergic receptors [26]. While these compounds lack hallucinogenic properties, they exhibit morphine-like narcotic effects. Consistent use can lead to dependence and withdrawal symptoms upon cessation, contributing to the addictive potential of kratom products [25]. At low doses, kratom produces stimulant-like effects, while higher doses induce sedation. Prolonged kratom use may result in drug dependence, characterized by severe physical symptoms (e.g., muscle spasms, pain, and insomnia) and psychological withdrawal manifestations (e.g., restlessness and nervousness) [27].

2.2. Drugs acting on ligand-gated ion channel-type receptors

2.2.1. Nicotine

Nicotine, the principal alkaloid found in tobacco plants, lacks clinical applications but remains a primary contributor to smoking addiction. Its mechanism of action primarily involves nicotinic acetylcholine receptors (nAChRs) in the brain, elevating DA levels through intricate interactions with receptors on GABA and DA neurons [9]. Additionally, nicotine enhances DA concentrations by inhibiting the enzyme monoamine oxidase, inducing sensations of pleasure and dependence in smokers [28].

2.2.2. Alcohol

Wine is produced through the fermentation of grains, with alcohol serving as its primary chemical component. Alcohol use disorder (AUD) represents a significant global health and public safety concern, ranking as the most prevalent substance use disorder (SUD) worldwide [29]. Unlike other addictive substances, alcohol's activation of the DA system is not attributed to a single mechanism; rather, it interacts with multiple ion channels on various receptors, including γ-aminobutyric acid type A ($GABA_A$) receptors, Kir3/GIRK and other K^+ channels, *N*-methyl-D-aspartic acid (NMDA) receptors, nAChRs, and others [6]. Studies indicate that the interplay between GlyRs and GABA receptors in the ventral striatum or VTA may underlie alcohol's ability to stimulate the dopaminergic system [30]. Additionally, alcohol can activate the reward system through the stimulation of 5-HT_3 receptors on dopaminergic neurons [9]. Prolonged excessive alcohol consumption can lead to various chronic diseases, with particularly detrimental effects on the heart, liver, and other vital organs.

2.2.3. BDZs and barbiturates

BDZs are synthetic prescription sedatives widely utilized for treating disorders such as anxiety, insomnia, and seizure control. However, they are increasingly subject to recreational abuse. BDZs function as positive allosteric modulators (PAM) of $GABA_A$ receptors, enhancing the firing of DA neurons in the VTA and elevating DA levels by positively modulating $GABA_A$ receptors in interneurons [31]. Analogous to BDZs, certain other drugs can interact with the modified regulatory sites of $GABA_A$ receptors, including barbiturates, neuroactive steroids, anesthetics, and ethanol. Barbiturates, which are anticonvulsants and were the first intravenous anesthetics, have largely been supplanted by BDZs due to their narrow therapeutic index and higher risk of overdose [32].

2.3. Drugs acting on the dopamine transporter (DAT)

2.3.1. Cocaine

Cocaine, an alkaloid extracted from coca leaves, functions as a psychostimulant. It primarily regulates DA levels by inhibiting its reuptake through the DAT. Additionally, cocaine modulates the release and reuptake of two other neurotransmitters: norepinephrine (NE) and serotonin (5-HT) [9]. Recent investigations have expanded our understanding of cocaine's potential mechanisms of action on NE. By modifying the net and downstream signaling of protein kinase C (PKC), which subsequently alters the activity of locus coeruleus-norepinephrine (LC-NE) neurons, cocaine directly increases the frequency of quantal NE release [33]. This insight presents a potential target for cocaine addiction

treatment. Initially, cocaine users experience symptoms such as euphoria, elevated mood, heightened cognitive activity, and increased mobility. Prolonged cocaine use can lead to adverse effects, including dizziness, anxiety, severe agitation, and restlessness, heightened sensitivity, mood fluctuations, insomnia, nausea, vomiting, and various mental disorders.

2.3.2. Synthetic psychostimulant

In addition to natural stimulants, synthetic amphetamines, such as methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA), are psychostimulants of widespread global abuse. Methamphetamine, a representative of this class, promotes the release of DA, 5-hydroxytryptamine, and NE [34]. Recognized mechanisms include: (1) enhancing DA synthesis by upregulating the expression of TH, a key enzyme in DA synthesis [35]; (2) inhibiting DA reuptake by suppressing the DAT and vesicular monoamine transporter (VMAT) [36]; and (3) reducing DA catabolism by inhibiting MAO. These mechanisms collectively increase extracellular levels of the aforementioned monoamine neurotransmitters, resulting in behavioral and neurotoxic effects. Amphetamine-type drugs exert potent hallucinogenic and CNS stimulant effects, manifesting as hyperactivity, fatigue insensitivity, emotional impulsivity, hypersexuality, heightened sociability, paranoia, delusions, reduced self-control, hallucinations, and increased propensity for violence [35]. Furthermore, intravenous administration can lead to various infectious comorbidities, including hepatitis, bacterial endocarditis, sepsis, and AIDS.

3. Addiction characteristics of classic drugs

The symptoms of addiction exhibit similar characteristics across various substances. For centrally acting addictive drugs, such as opioids, initial ingestion triggers a reinforcing effect, namely tolerance, in the early stages of addiction development. During this phase, the drug's effects diminish with repeated use, necessitating increased dosage or frequency to achieve the initial effect. Prolonged use of addictive substances can significantly impair a patient's health and social functioning. The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) classifies these symptoms under SUD [37]. The most severe form of SUD manifests after the development of addictive symptoms, characterized by compulsive substance use, loss of control over intake quantities, and negative emotional states when deprived of the substance [38].

The development of addiction symptoms during substance abuse can be broadly categorized into three stages: obsession and anticipation, withdrawal and depression, and binge and intoxication [13]. Each stage corresponds to the activation of specific brain circuits. Addictive substances trigger a rapid release of DA in the brain's reward areas, initiating associative learning or conditioning [9]. With repeated exposure to the same reward, DA cells begin to respond to conditioned stimuli ("cues") that predict reward delivery, rather than to the reward itself [38]. Consequently, exposure to relevant cues (such as environment, peers, or mental state) can elicit a rapid increase in DA release, prompting drug craving and seeking behavior [38]. Chronic exposure to the DA-enhancing effects of most drugs alters the extended amygdala circuits in the basal forebrain, leading to heightened reactions to stress and negative emotions in addicts [39]. This "anti-reward" system is driven by neurotransmitters involved in the stress response, including dynorphins and adrenocorticotropin-releasing factor (ARF), which typically maintain homeostasis [37]. As the direct effects of the drug subside, the anti-reward system becomes hyperactive, resulting in decreased responsiveness of DA cells in the reward circuitry [40]. This leads to increased tension and anxiety in the patient, who then develops another craving for the drug to alleviate these symptoms, thus perpetuating a vicious cycle (Fig. 2).

4. Pharmacotherapy for drug addiction

The drugs and active compounds currently under investigation will be categorized and presented based on their respective therapeutic targets (Table 1 and Fig. 3).

4.1. Opioid receptor modulators

In the treatment of drug addiction, severe withdrawal reactions significantly contribute to treatment failure and relapse. Opioid receptor agonists are primarily utilized in substitution therapy, aiming to achieve therapeutic outcomes by replacing exogenous opioid compounds and gradually reducing the drug dose to normalize endogenous opioid peptide levels. Methadone, a classical drug employed in substitution regressive therapy and maintenance therapy, still faces challenges in practical application due to its addiction potential and associated social issues [41]. Buprenorphine, an opioid receptor partial agonist approved for opioid addiction treatment in 2002, has shown poor patient adherence in subsequent studies [65]. Adherence can be enhanced through longer-acting preparations, such as buprenorphine implants, which maintain therapeutic levels for up to 6 months but require surgical insertion and removal. Additionally, a wide range of buprenorphine products in advanced development stages offer weekly and monthly injections without surgical insertion, providing greater flexibility in treating opioid use disorder [66].

Opioid receptor antagonists are primarily utilized in the management of acute intoxication resulting from opioid addiction. These agents mitigate respiratory depression and other symptoms associated with acute intoxication by blocking opioid receptors and are generally employed as adjunctive therapy. For instance, the combination of naloxone (an opioid receptor antagonist) with buprenorphine (a partial opioid receptor agonist) serves to deter the intravenous misuse of buprenorphine, and various buprenorphine/naloxone formulations have been commercialized [66]. When patients adhere to prescribed oral administration, naloxone's effects are minimal. However, if intravenous administration is attempted to achieve euphoria, naloxone induces withdrawal symptoms by antagonizing opioid receptors, thereby preventing intravenous abuse. Naltrexone is a commonly prescribed opioid receptor antagonist in clinical practice. To enhance medication adherence, the FDA approved a monthly inject-

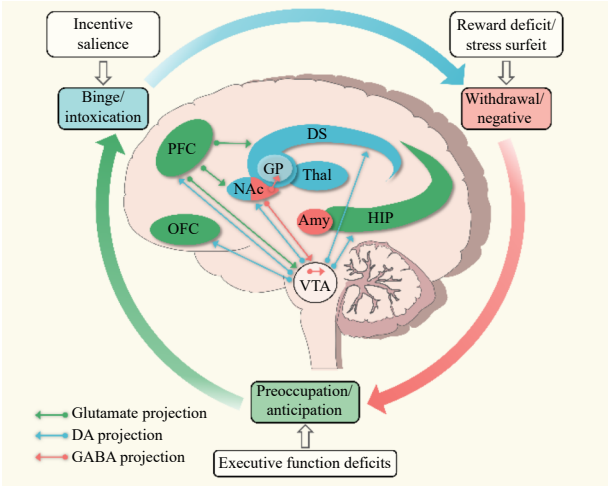

Fig. 2 The three-stage cycle of addiction and related brain regions. PFC, prefrontal cortex; OFC, orbitofrontal cortex; NAc, nucleus accumbens; DS, dorsal striatum; GP, globus pallidus; Thal, thalamus; Amy, amygdala; HIP, hippocampus; VTA, ventral tegmental area.

Table 1 Representative pharmacotherapy for addiction.

Drug	Type	Mechanisms
Methadone/Buprenorphine	Opioid receptor agonist	Substitution of opioids with gradual dose reduction to restore endogenous opioid peptides to normal levels [41].
Naltrexone	Opioid receptor antagonist	Rescue from acute poisoning by opioid addiction [42].
AT-121/BU08028	Bifunctional NOP/MOP agonist	Simultaneous activation of MOP and NOP receptors synergistically enhances μ-opioid peptide receptor-mediated effects [43–44].
Brexpiprazole/Aripiprazole	DA receptor agonist	Acting on D_2 and D_3 receptors and 5-$HT_{1A/2A}$ receptors to reduce increased NAc DA levels [45].
Paliperidone/GSK598809	DA receptor antagonist	Antagonizing central D_2 and/or D_3 receptors and dose-dependently reduces self-administration [46–47].
Bupropion	DA/NE reuptake inhibitor	Inhibiting the reuptake of DA and NE and can be used in combination with varenicline and dextromethorphan [48].
CTDP-32476/RTI-336	DAT regulator	Modulation of the effects of addictive drugs on NAc DA through inhibitory or metamorphic modulatory effects on DAT [49–50].
Psilocybin/Ibogaine/Tabernanthalog	5-HT_{2A} receptor modulator	Exerts psychedelic effects *via* 5-HT_{2A} receptors and may also be involved in anti-addictive processes by modulating neuroplasticity [51,22].
Lorcaserin	5-HT_{2C} receptor agonist	Acting by agonizing 5-HT_{2C} receptors, but whether it has a definitive therapeutic effect on addiction requires continued research [52].
Vortioxetine/Mirtazapine	5-HT receptor modulator	Acting on receptors 5-HT_1, 5-HT_{2A}, 5-HT_3, and 5-HT_7, downregulates DA levels, and reduces cocaine-induced motor sensitization [53–54].
Memantine	NMDA receptor antagonist	Transiently blocking NMDA receptors and reduces glutamatergic overstimulation, but may be ineffective in low glutamatergic states [55].
Topiramate/Lamotrigine/Riluzole	AMPA receptor antagonist	Dose-dependent inhibition of cue-induced relapse reverses the inhibitory effect of cocaine on NAc GLT-1 [56–57].
LY379268/AZD8529/JNJ16259685	mGluRs agonist	Reduction of self-administration and cue-induced relapse by agonistic/antagonistic/mutagenic modulation of mGluRs [58–59].
Rimonabant/AM4113/CBD	CB_1 receptor antagonist	Attenuating cue-induced drug-seeking behavior by antagonizing CB1 receptors involved in addictive neural circuits [60–61].
AEF0117	CB_1-SSI	Selectively inhibits intracellular effects induced by THC binding without being psychoactive itself [62].
Exenatide/Semaglutide	GLP-1R agonists	Acting on the GLP-1R of VTA and NAc to attenuate the rewarding effects of drugs and withdrawal symptoms [63–64].

Abbreviations: NOP, nociceptin/orphanin peptide; MOP, μ-opioid peptide; DA, dopamine; 5-HT, 5-hydroxytryptamine; NE, norepinephrine; DAT, dopamine transporter; NMDA, *N*-methyl-D-aspartic acid; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; NAc, nucleus accumbens; GLT-1, glutamate transporter-1; mGluRs, metabotropic glutamate receptors; CB1-SSI, signaling-specific inhibitors of CB_1; THC, tetrahydrocannabinol; GLP-1R, glucagon-like peptide-1 receptor; VTA, ventral tegmental area.

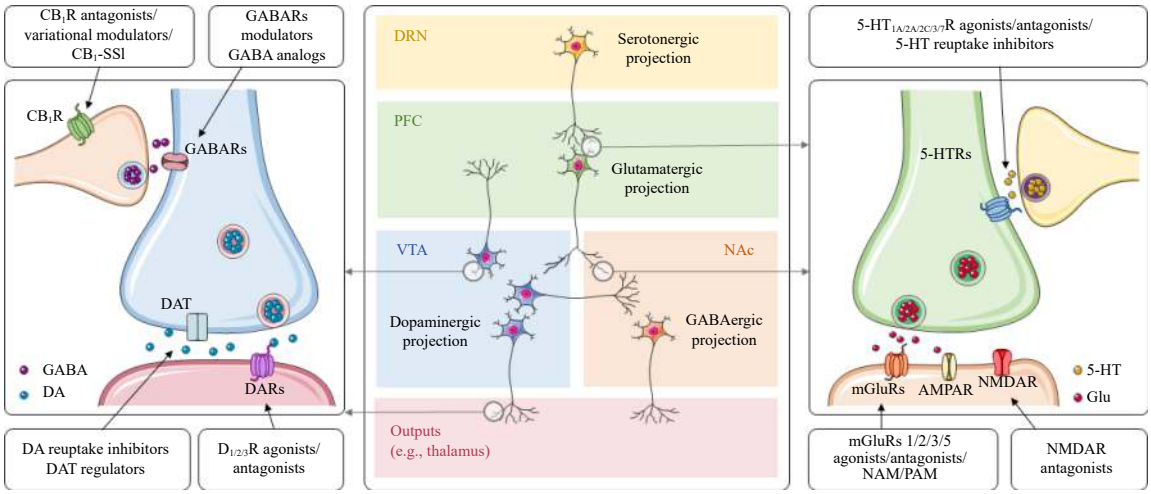

Fig. 3 Major therapeutic targets and corresponding therapeutic drug classes in the mesocorticolimbic pathway. CB_1R, cannabinoid receptors 1; GABA, γ-aminobutyric acid; GABARs, γ-aminobutyric acid receptors; DA, dopamine; DAT, dopamine transporter; DARs, dopamine receptors; DRN, dorsal raphe nucleus; PFC, prefrontal cortex; VTA, ventral tegmental area; NAc, nucleus accumbens; 5-HT, 5-hydroxytryptamine; 5-HTRs, 5-hydroxytryptamine receptors; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate receptor; NMDAR, *N*-methyl-D-aspartic acid receptor; PAM, positive allosteric modulator; NAM, negative allosteric modulator.

able formulation of naltrexone (Vivitrol®) for relapse prevention, based on findings from a double-blind, placebo-controlled clinical trial [42].

Beyond the conventional μ, κ, and δ receptors, opioids also interact with NOP receptors. Research has highlighted the analgesic and therapeutic potential of bifunctional NOP/MOP agonists in addressing opioid abuse. For instance, AT-121 significantly mitigated oxycodone-induced potentiation [44], while BU08028 selectively decreased alcohol consumption in rhesus monkeys [43]. These findings underscore the promising therapeutic applications of bifunctional NOP/MOP partial agonists in treating substance abuse, particularly opioid addiction [11].

In conclusion, while numerous opioid receptor-based medications are available for addiction treatment, they present several limitations. These include poor compliance and inadequate amelioration of critical aspects of addiction, such as relapse triggered by conditioned associations (e.g., cues, stress). Notably, opioid receptor agonists are inherently addictive, possess a narrow therapeutic window, and require strict adherence to dosage and treatment regimens [41]. Consequently, there is a pressing need to explore alternative key sites within the mechanisms of drug addiction to identify potential therapeutic targets.

4.2. DA modulators

The initiation and progression of drug addiction are intricately linked to the DA system. Consequently, pharmaceuticals that regulate DA levels in pertinent brain regions show promise

as potential treatments for drug addiction. These may include DA receptor agonists and antagonists, DAT modulators, and DA reuptake inhibitors.

4.2.1. DA receptor agonists/antagonists

DA receptors comprise five subtypes: D_1, D_2, D_3, D_4, and D_5. The D_1 class of receptors, which includes D_1 and D_5, is associated with the reward mechanism of addiction [67]. The D_2 class, encompassing D_2, D_3, and D_4 receptors, plays a crucial role in the addiction process. Notably, reduced expression of the D_2 receptor correlates with an increased risk of drug addiction and relapse [68]. The D_3 receptor, highly expressed in brain regions related to reward, represents a significant target for addiction research [69].

DA receptor agonists can restore dopaminergic signaling during drug withdrawal while mitigating associated adverse effects [70]. Brexpiprazole, a partial agonist at D_2 and D_3 receptors, has received approval for treating schizophrenia and major depressive disorder [71]. While brexpiprazole and its predecessor, aripiprazole, exhibit similar affinity for DA receptors, brexpiprazole demonstrates higher affinity for 5-$HT_{1A/2A}$ and lower activity at D_2 receptors [70]. Previous studies have shown that aripiprazole attenuates the recovery of conditioned place preference (CPP) and drug-seeking behaviors, as well as reduces morphine-induced increases in nucleus accumbens (NAc) DA levels [72]. Recent investigations have explored brexpiprazole's behavioral effects on opioid dependence and withdrawal. The compound modulates sensitization and drug-seeking-related behaviors in opioid addiction, as well as opioid-induced nociceptive sensitization, providing preclinical evidence for its potential use in treating the sustained drug craving phase of addiction [45]. Clinical trials have demonstrated brexpiprazole's efficacy in treating schizophrenia co-occurring with SUD, significantly improving patients' quality of life. Additionally, it exhibits a favorable safety and tolerability profile, with no major side effects reported [73].

DA receptor antagonists inhibit dopaminergic neuronal transmission and attenuate addiction-related behaviors in animal models, including methamphetamine-induced behavioral sensitization, CPP, and self-administration [74]. Chen et al. combined paliperidone long-acting injection, a D_2 receptor antagonist, with electroacupuncture therapy. This integrated approach demonstrated enhanced efficacy, significantly improving anxiety, depression, and brain wave patterns, thereby reducing the risk of relapse [46]. Additionally, the D_1 receptor antagonist SCH23390 has shown efficacy in diminishing methamphetamine- and cocaine-induced CPP, potentially inhibiting the development of DA receptor hypersensitivity [47].

The increased expression of the D_3 receptor in the addicted state indicates its significant role in the neurological mechanisms underlying drug addiction, suggesting that D_3 receptor inhibition may mitigate cravings and prevent relapse. In *in vivo* studies, GSK598809, a D_3 receptor antagonist, demonstrated dose-dependent attenuation of nicotine-induced CPP in rats and temporarily alleviated cravings in smokers during clinical trials [75]. However, research has revealed that GSK598809 enhances the hemodynamic effects of cocaine in animal models, indicating that this class of D_3 receptor antagonists may pose cardiovascular risks when used as a treatment for cocaine use disorders [76].

4.2.2. DA reuptake inhibitors

Bupropion, a reuptake inhibitor of DA and NE, has demonstrated a significant reduction in nicotine self-administration [48]. Current research focuses on combining bupropion with other medications to treat addiction. The combination of bupropion and dextromethorphan (AXS-05) for treating depression and Alzheimer's disease (AD) has progressed to clinical trials [77]. Dextromethorphan, a 5-HT reuptake inhibitor, exhibits increased brain activity when its metabolism is inhibited by bupropion, enhancing the combination's efficacy. Clinical trials have shown that AXS-05 improves depressive symptoms, outperforms bupropion alone, and is generally well-tolerated, with potential mild to moderate side effects including dizziness, nausea, dry mouth, decreased appetite, and anxiety [78]. A recent study revealed that bupropion significantly decreased opioid use in rats with higher baseline levels. However, it increased remifentanil use in rats with lower initial administration, indicating complex effects of the bupropion-dextromethorphan combination on remifentanil self-administration [79]. Further investigation into the differential effects of this combination therapy on mild and heavy opioid users is warranted.

4.2.3. DAT regulators

Agonist substitution therapy has demonstrated efficacy in treating opiate and nicotine addiction. However, applying this approach to cocaine addiction presents significant challenges, primarily due to the inherent cocaine-like effects and addictive potential of the agonists used in substitution therapy. It is widely accepted that a drug's addictive propensity correlates with the rapidity of its onset of action. Substances that rapidly reach the brain typically possess higher addictive potential. Consequently, DAT regulators intended for treating cocaine addiction must exhibit slow-acting properties and prolonged duration of action [80].

CTDP-32476, a piperidine compound, exhibits notable characteristics, including stable metabolism, gradual onset of action, and prolonged duration of effect. These properties suggest its potential as a treatment for cocaine addiction. This compound functions as a potent and selective DAT regulator, effectively counteracting cocaine's impact on extracellular DA levels in the NAc. Importantly, CTDP-32476 demonstrates a significantly reduced addiction potential compared to cocaine [81].

RTI-336, a 3-phenyltropane analog, is a DAT-selective inhibitor that has demonstrated efficacy in reducing cocaine self-administration in rat and rhesus monkey models, with a low propensity for abuse [49]. Clinical trials further confirmed its favorable safety profile, with all tested doses including the highest dose exhibiting good tolerability and no serious adverse effects, paving the way for further human studies [82].

4.3. 5-HT receptor modulators

As described in 2.1.3, classical hallucinogens primarily exert their psychedelic effects through 5-HT_{2A} receptors. Nevertheless, these substances demonstrate potential for modulating brain function and treating psychiatric disorders. The past decade has witnessed an increase in clinical studies examining psilocybin's efficacy in treating various psychiatric conditions, including depression, anxiety, cognitive deficits, and SUD [22]. Several clinical trials have demonstrated the therapeutic efficacy of psilocybin-assisted treatment for alcohol and tobacco addiction [83]. Ibogaine, an indole-type alkaloid derived from *Tabernanthe iboga*, has shown promise in reducing drug withdrawal symptoms, cravings, and relapse, with potential applications in treating addictions to opioids, alcohol, and psychostimulants [51]. However, ibogaine's hallucinogenic properties and adverse effects have impeded its further development. Recent research has led to the design and synthesis of tabernanthalog, a non-hallucinogenic, non-toxic analog of ibogaine. In rodent studies, tabernanthalog promotes neuroplasticity and reduces alcohol- and heroin-seeking behaviors [51]. This development suggests that modifying hallucinogenic compounds may yield safer, non-hallucinogenic alternatives with therapeutic potential.

Extensive preclinical research has highlighted the therapeutic potential of 5-HT_{2C} receptor agonists in addressing drug addiction. Lorcaserin, a selective 5-HT_{2C} receptor agonist, recently gained FDA approval for weight management. Studies have

shown that lorcaserin dose-dependently diminished self-administration of various substances, including psychostimulants and opioids such as nicotine, alcohol, marijuana, and cocaine, as well as relapse triggered by drug-associated cues [84]. Multiple clinical trials investigating lorcaserin's efficacy in treating addiction to these substances are currently in progress. A placebo-controlled clinical study revealed that lorcaserin significantly reduced self-administration and cravings following marijuana withdrawal [52]. However, numerous studies have also reported ineffective outcomes. One human study found that lorcaserin (10 mg, b.i.d.) did not effectively decrease the propensity to abuse oxycodone [85]. Another study examining lorcaserin in conjunction with cocaine in cocaine-dependent individuals demonstrated a reduction in subjective ratings of cocaine craving correlated with lorcaserin dosage, but failed to diminish cocaine's reinforcing effects [86]. The most frequently reported adverse effects of lorcaserin included dizziness, nausea, and fatigue. Additionally, psychoactive effects such as "detachment" and "floating" were observed in subjects at supratherapeutic doses (20–60 mg), potentially attributed to 5-HT_{2C} receptor activity [84]. Further research is necessary to conclusively establish the efficacy of 5-HT_{2C} receptor agonists as viable treatments for drug addiction.

In addition to the 5-HT_{2A} and 5-HT_{2C} receptors, numerous other subtypes of the 5-HT receptor family are implicated in drug addiction, including 5-HT_1, 5-HT_3, and 5-HT_7 receptors [87–88]. Consequently, multi-targeted 5-HT modulators represent a promising avenue for future research. Several 5-HT multi-target modulators, initially approved for treating depression and other disorders, have progressed to preclinical or clinical trials for drug addiction treatment. Vortioxetine, an antagonist of 5-HT_3 and 5-HT_7 receptors and an agonist of 5-HT_{1A} receptors, was found by Barbosa-Mendez et al. to reduce cocaine-induced motor sensitization and downregulation of DA levels [53]. Mirtazapine, which agonizes 5-HT_{1A} receptors and antagonizes 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptors, demonstrated reduced cocaine-induced locomotor activity and motor sensitization in both preclinical and clinical trials [54]. These findings suggest that multi-target modulators may offer a potential therapeutic approach for treating cocaine and other drug addictions.

4.4. Glutamate receptor modulators

Glutamate is a crucial neurotransmitter that plays a significant role in regulating neuroplasticity and other neurological functions through ionotropic glutamate receptors and metabotropic glutamate receptors (mGluRs). Ionotropic glutamate receptors are ligand-gated ion channels classified into three subtypes: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), erythrocyanine, and NMDA [89]. mGluRs, which are GPCRs with seven transmembrane regions, encompass various isoforms. Among these, the mGluRs of group I (mGluR1 and mGluR5) and group II (mGluR2 and mGluR3) have been strongly associated with the process of drug addiction. Researchers have developed several compounds targeting these receptors to address addiction-related issues.

Memantine, a medication that targets NMDA receptors, has demonstrated efficacy in preclinical studies for reducing alcohol dependence, cocaine-seeking behavior, and cocaine-induced CPP. While clinical studies have yielded some inconsistent results, numerous investigations have substantiated memantine's effectiveness in diminishing alcohol, cocaine, and opioid use, as well as alleviating cravings and withdrawal symptoms [55]. When administered alone or as an adjunct to methadone or buprenorphine, memantine effectively reduces opioid cravings, enhances patients' cognitive function, and is generally well-tolerated. Commonly reported side effects include insomnia, mood alterations, fatigue, and changes in appetite [90]. Current research on AMPA receptor antagonists for treating drug addiction has primarily focused on antiepileptic medications such as topiramate and lamotrigine [56]. However, due to concerns regarding efficacy and adverse effects, there is a pressing need to identify novel therapeutic agents. Riluzole has shown promise in preclinical studies, demonstrating dose-dependent inhibition of cue-induced relapse and reversal of cocaine-induced reward effects. Additionally, it counteracts the inhibitory effect of cocaine on NAc glutamate transporter-1 (GLT-1), potentially offering a therapeutic alternative to conventional antiepileptic drugs [57].

The mGluRs 2/3 agonist LY379268 demonstrates efficacy in reducing self-administration and cue-induced relapse for heroin, cocaine, and methamphetamine [59]. Justinova et al. observed that AZD8529, a selective orthosteric modulator of mGluR2, diminished self-administration and cue-induced relapse to nicotine in monkeys while decreasing nicotine-induced DA release from the NAc in rats [59]. The mGluR1 antagonist JNJ16259685 was found to attenuate cue-induced cocaine-seeking recovery in preclinical studies [58]. Additionally, preclinical research indicates that NAM of mGluR5 reduced cocaine self-administration and inhibited cue-induced relapse [91]. These findings collectively suggest that modulators of mGluRs hold promise for potential applications in the treatment of drug addiction and relapse prevention.

4.5. CB_1 receptor regulators

A growing body of research in both animal models and human subjects has demonstrated the potential efficacy of CB_1 receptor antagonists in treating drug addiction. In 2006, rimonabant (SR141716, AComplia®), a first-generation CB_1 receptor antagonist, was introduced in the United Kingdom for diabetes and obesity management [92]. Additionally, it showed promise in facilitating smoking cessation [93]. However, rimonabant was withdrawn from the European market in 2008 due to severe psychiatric side effects, including depression, anxiety, and suicidal ideation. Other adverse effects associated with CB_1 receptor antagonists include an increased incidence of headaches, insomnia, dizziness, nausea, vomiting, and pruritus. Consequently, other CB_1 receptor antagonists undergoing clinical trials were also discontinued [94].

To minimize or eliminate the adverse effects of CB_1 receptor antagonists while maintaining their therapeutic efficacy, researchers are developing novel CB_1 receptor-targeted inhibitors. These include neutral antagonists, peripherally restricted antagonists, and variational modulators. One such example is AM4113, a pyrazole analog that functions as a neutral antagonist of the CB_1 receptor. Numerous studies have demonstrated AM4113's therapeutic potential for opioid, nicotine, cannabis, and alcohol addiction [95–96]. Research indicates that AM4113 reduces nicotine- and THC-seeking behaviors, as well as cue-induced reinstatement of cocaine self-administration in a primate model of addiction. Importantly, it exhibits fewer adverse effects typically associated with CB_1 receptor antagonists [61].

Concurrently, investigations into other cannabinoid-related compounds persist. CBD functions as a mild CB_1 receptor antagonist, influencing central and peripheral neurotransmission without inducing psychoactive effects comparable to THC [21]. Research suggests CBD may have potential therapeutic applications for opioid, marijuana, psychostimulant, and tobacco addictions. However, additional clinical trials are necessary to substantiate CBD's efficacy as a treatment modality for SUD [60, 97].

Recent research has introduced a novel pharmacological class of CBD termed signaling-specific inhibitors of CB_1 (CB_1-SSI). AEF0117, the inaugural CB_1-SSI, is currently undergoing clinical trials. This compound exhibits a distinctive mechanism of action, selectively inhibiting intracellular effects induced by Δ^9-THC binding without demonstrating psychoactive properties [62]. Stud-

ies indicate that AEF0117 diminished cannabinoid self-administration and THC-related behaviors while demonstrating good tolerability in clinical trials, with no apparent adverse effects [98]. These findings suggest that AEF0117 may reduce marijuana abuse without interfering with normal physiological functions.

4.6. Glucagon-like peptide-1 receptor (GLP-1R) agonists

GLP-1R agonists, approved by the FDA for treating type II diabetes mellitus and obesity, have demonstrated involvement in addiction neurobiology. GLP-1R expression in the VTA and NAc regions, which are associated with drug-induced reinforcement, suggests a potential role in addiction treatment. Studies indicate that GLP-1R agonists diminish the rewarding effects of various substances, including alcohol, cocaine, amphetamines, and nicotine [99]. Research by Yammine et al. revealed that exenatide, an extended-release GLP-1R agonist, when combined with nicotine replacement therapy, enhanced smoking cessation rates, reduced cravings and withdrawal symptoms, and mitigated post-cessation weight gain compared to nicotine replacement therapy alone [64]. Although a clinical trial showed that exenatide did not significantly reduce alcohol consumption, it notably attenuated fMRI alcohol cueing responses in the VTA and NAc, and decreased DAT utilization [100]. Furthermore, evidence suggests that peripheral administration of GLP-1 receptor agonists diminishes cocaine-induced CPP and behavioral sensitization [101]. Common adverse events reported in clinical trials include gastrointestinal symptoms, weight loss, fatigue, and injection site reactions [64].

Semaglutide, one of the most recently FDA-approved long-acting GLP-1 analogs, demonstrates enhanced GLP-1R binding and superior clinical efficacy [102]. A recent investigation revealed that semaglutide reduced alcohol consumption in mice and dependence-induced drinking in rats in a dose-dependent manner while modulating central GABA neurotransmission [63]. These findings provide compelling evidence supporting the potential of GLP-1R modulators as pharmacotherapeutic targets for SUD.

4.7. Other pharmacotherapy

Beyond the aforementioned drug categories, researchers have identified numerous potential options for treating drug addiction. These include glial modulators based on phosphodiesterase type 4 (PDE4) inhibitors, various GABA modulators, and other pharmacological agents. Table 2 presents detailed information about these compounds. It is important to note that the majority of these drugs are still in clinical or preclinical research phases, indicating certain limitations. Nevertheless, they undoubtedly provide a foundation for developing novel pharmacotherapies for substance addiction. Consequently, further research and development in this area are imperative to advance these potential treatments.

5. Traditional Chinese medicine therapy for drug addiction

Numerous natural substances have been investigated for their potential in treating addictions. CBD, derived from cannabis, has shown promising therapeutic effects on opioid, psychostimulant, and tobacco addiction [97]. Tetrodotoxin, an alkaloid found in triggerfish, is currently undergoing Phase II clinical trials for its potential in treating opioid addiction [106]. Cytisine, an alkaloid extracted from leguminous plants, has been utilized for smoking cessation, primarily targeting nAChRs, and has been approved for this purpose in several European countries for decades [111]. Both xylosabine and ibogaine, as described in section 4.3, demonstrate therapeutic effects on drug addiction. L-tetrahydropalmatine (L-THP), extracted from Corydalis Rhizoma (Yanhusuo), exhibits significant anti-addictive properties and may attenuate rewarding effects by blocking DA receptors [112]. Active ingredients in Chinese herbs such as Ginseng Radix et Rhizoma (Renshen), Uncariae Ramulus Cum Uncis (Gouteng), Polygoni Cuspidati Rhizoma et Radix (Huzhang), and Astragali Radix (Huangqi) have also demonstrated positive effects in treating methamphetamine addiction [113]. Herbal compounding, leveraging a diverse array of beneficial ingredients, represents a promising future direction in addiction drug development. For instance, Jitai Tablet, an herbal compound preparation, is used to alleviate opioid addiction withdrawal symptoms. It effectively controls delayed symptoms, inhibits drug-seeking behaviors associated with psychological dependence, and exhibits preventive effects on opioid relapse [114]. Traditional Chinese medicine offers a multi-target approach to addiction intervention, with low addictive potential and minimal toxic side effects, positioning it as a valuable complementary approach to modern drug treatments [113].

6. Immunotherapy for drug addiction

The development of therapeutic drugs for addiction has historically faced challenges, including limited efficacy and significant side effects. Recently, anti-addiction vaccines based on immunological principles have emerged as a promising approach, demonstrating the ability to mitigate rewarding effects or reduce cravings associated with drug use while minimizing side effects. Given that small molecules such as cocaine and heroin typically do not elicit an immune response independently, drugs of abuse or their analogues must be conjugated to immunogenic proteins to enable the immune system to recognize these substances and produce specific antibodies [115]. These antibodies identify and sequester drugs circulating in the bloodstream, thereby reducing

Table 2 Status of research on other pharmacotherapy for addiction treatment.

Drug	Clinical indications	Type	Current results	Phase
Lofexidine	Opioid withdrawal syndrome	$\alpha 2$-Adrenergic receptor agonist	Significantly reduced SOWS scores and showed better retention and a favorable safety profile among participants in opioid withdrawal [103].	Phase III
Apremilast	Psoriasis, alcoholism	PDE4 inhibitor	Behavioral indicators of alcohol intake and alcohol motivation in the reducing alcoholism sample. Reducing excessive drinking in models of alcohol dependence [104].	Phase II
Ibudilast	Asthma, opioid addiction, alcoholism	PDE4 inhibitor	Inhibition of glial cell activation alters opioid-mediated analgesia and withdrawal symptoms [105].	Phase II
Tetrodotoxin	Opioid addiction, neuropathic pain, cancer pain	Sodium channel blocker	Patients experienced a dose-dependent decrease in craving and anxiety levels and a significant increase in remission of opioid withdrawal syndrome [106].	Phase II
ASP8062	Opioid addiction, alcoholism	$GABA_B$ PAM	Suppression of opioid and alcohol self-administration with favorable clinical safety and pharmacodynamic effects [107].	Phase II
Gabapentin	Epilepsy, neuropathic pain, cannabinoid addiction	GABA analogs	Clinically reduced the number of days of alcohol use in patients with lower AUDIT-C scores [108]. Effective treatment of cannabinoid withdrawal symptoms, including somatic and affective symptoms [109].	Phase II/Preclinical
CPP-115	Cocaine addiction, epilepsy, infantile spasms	GABA aminotransferase inactivator	Inhibits cocaine-induced increase in NAc DA and blocks cocaine-induced CPP. Similar effects can be achieved with smaller doses compared to comparable drugs [110].	Phase I

Abbreviations: PDE4, phosphodiesterase type 4; GABA, γ-aminobutyric acid; PAM, positive allosteric modulator.

the permeability of the drugs across the blood-brain barrier and effectively attenuating the CNS psychoactive effects associated with abuse [116]. Despite numerous preclinical studies yielding satisfactory results, few vaccines have successfully progressed to clinical trials [117]. Table 3 presents several representative vaccines and their current research status.

Table 3 Current status of research on representative immunotherapies for drug addiction.

Vaccine	Clinical indications	Composition (haptens and carriers)	Current results	Phase
TA-CD	Cocaine addiction	Succinyl de cocaine and rCTB	A significant relationship between attaining high antibody levels and reduced cocaine use [118].	Phase II/III
NicVax	Nicotine addiction	Nicotine and pseudomonas aeruginosa exogenous protein A	The binding of nicotine to nAChRs was reduced [119]. Does not increase smoking cessation rates in the clinic [120].	Phase II/III
Oxy(Gly)4-sKLH	Oxycodone addiction	Oxycodone is attached to KLH *via* tetraglycine	Induces persistent antibodies that significantly reduce the potentiating effects of oxycodone [121].	Phase I/II
dAd5GNE	Cocaine addiction	Cocaine analog GNE and disrupted adenovirus capsid protein	Obstructs the entry of cocaine into the central system to bind to DAT. Reduces the effects of cocaine on the nervous system and organs [122].	Phase I

Abbreviations: rCTB, cholera toxin B; KLH, keyhole limpet hemocyanin.

To address limitations and enhance immunogenicity, researchers have adopted various innovative approaches to vaccine design. These include optimizing carrier proteins to increase the immunogenicity of conjugated vaccines, designing nanoparticles to improve antigen presentation, synthesizing semi-antigens, and developing more potent adjuvants [116]. By refining vaccine design strategies, researchers can better predict vaccine responses and identify potential markers of addiction. These advancements will contribute to the further development of immunotherapies for the treatment of SUD.

7. Conclusions and prospects

Drug addiction remains a paramount concern in contemporary scientific research. While the mesocorticolimbic DA system's significance in addiction is well-established, the precise roles of specific neural circuits and other neurotransmitters in the addiction process require further elucidation. Moreover, additional comprehensive research is necessary to explicitly delineate how genetic predisposition, individual variability, and environmental factors influence addiction susceptibility, the long-term neurological consequences of addiction, and the mechanisms of post-withdrawal recovery. Currently, several treatment modalities are available for substance abuse, including opioids, alcohol, and nicotine, such as substitution therapy, cognitive-behavioral therapy, and social interventions. However, the efficacy of these treatments is contingent upon multiple factors, necessitating ongoing investigation and refinement.

This work synthesizes recent advances in the study of mechanisms and therapeutic interventions for drug addiction. Comprehensive investigations into DA, glutamate, and other neurotransmitters have elucidated their specific roles in the addiction process. Advancements in brain imaging technology have enabled researchers to identify that drug addiction induces plastic changes in the brain, including altered neuronal connectivity and enhanced synaptic transmission. Concurrently, novel therapeutic targets and drugs continue to emerge, with some demonstrating efficacy in addiction treatment. Future research should focus on determining the clinical effects and side effects of these drugs to provide new options for treating drug addiction. This research is crucial for the prevention and treatment of drug addiction, the development of less addictive drugs for anesthesia, analgesia, and psychiatric disorders, and to address the challenges posed by evolving new psychoactive substances (NPS).

Given the intricate effects of drugs on the central nervous system, the development of promising combination therapies continues, addressing the limitations of current treatment modalities. For instance, combining pharmacological interventions with transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS) shows potential in addiction treatment. Emerging therapeutic approaches such as immunotherapy, optogenetics, and brain-computer interface technology represent future trends that may enhance intervention and treatment efficacy for addictions. Furthermore, genomics and other biomarkers could potentially facilitate the development of personalized treatment protocols, potentially improving outcomes and minimizing adverse effects.

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Declaration of competing interest

These authors have no conflict of interest to declare.

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The cover design highlights the origin and development of psychoactive substances. Addictive substances were initially extracted from *Papaver somniferum*, marijuana and other raw plants, and the chemical structures of the psychoactive substances that lead to addiction were obtained through the isolation and corroboration of the extracted alkaloids. Subsequently, more harmful semi-synthetic and synthetic drugs are derived through structural modification and synthesis. The picture reflects the natural sources, chemical structures and common forms of addiction to addictive substances, the abuse of which is a major problem jeopardizing public safety and human health. Therefore, research on the specific mechanisms of drug addiction and its treatment is of great significance. This review describes the sources and pharmacological mechanisms of addiction to natural psychoactive substances and outlines research advances in the treatment of drug addiction.