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Review

Emerging Therapeutics in the Treatment of Substance Use Disorders: A Focus on GLP-1 Receptor Agonists, D3R Antagonists, and CRF Antagonists

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Abstract

The prevalence and rising use of alcohol, opioids, and stimulants have led to substance use disorders (SUDs) that are a significant public health challenge. Traditional treatments offer some benefit; however, they often limited by efficacy, side effects, and accessibility, highlighting the urgent need for novel therapeutics. This review explores the current literature surrounding three different classes of novel treatments: glucagon-like peptide-1 (GLP-1) receptor agonists, dopamine D3 receptor (D3R) antagonists, and corticotropin-releasing factor (CRF) antagonists. These therapeutics collectively target different aspects of the addiction process, such as stress and relapse prevention, reward modulation, and the reduction of drug-seeking behavior, leading to a combined multifaceted approach to treating SUDs. This review includes preclinical and clinical evidence supporting the use of these therapies, highlighting their potential to reduce substance use and prevent relapse to alcohol, opioid, and stimulant use. Despite the potentially promising findings of these treatments, further research is necessary to fully understand their mechanisms, optimize their application, and confirm their efficacy in clinical settings.

Keywords: novel therapeutics; alcohol; opioid; stimulants; glucagon-like peptide-1 receptor (GLP-1) agonists; dopamine D3 receptor (D3R) antagonists; corticotropin-releasing factor (CRF) antagonists

1. Introduction

Substance use disorders (SUDs) can be defined as persistent and problematic patterns of substance use that lead to significant clinical impairment or distress, characterized by impaired control, social impairment, risky use, and signs of physical dependence [1]. These disorders represent a significant public health crisis, with substantial economic burden [2]. According to a 2020 report by the United Nations Office on Drugs and Crime, 269 million people in the world use drugs and 35 million of those have a substance use disorder [3]. In 2023, in the United States alone, an alarming 17 percent of the population, or over 48 million people aged 12 or older, had a SUD in the past year, with alcohol, opioids, and stimulants being the most misused substances [4].

This review focuses on three major SUDs: alcohol use disorder (AUD), opioid use disorder (OUD), and stimulant use disorder (StUD). These disorders were selected due to their high prevalence, significant public health impact, and the urgent need for effective treatments [4]. While other substance use disorders, such as cannabis or tobacco use disorders also pose significant health challenges, the severity and complexity of AUD, OUD, and StUD, along with the current gaps in treatment, make them critical areas of focus [4].

Among all SUDs, AUD is the most prevalent with 400 million people aged 15 and older affected globally, according to data from the WHO in 2019 [5]. In the United States, AUD affected 28.9 million people aged 12 or older in 2023, with age-standardized death rates seeing an increase of 17.5% from 1990 to 2016 and costing the American economy a quarter of a trillion dollars in 2010 [4,6]. Chronic and/or heavy alcohol use has been shown to have adverse health outcomes including cardiovascular disease, gastrointestinal disease, infectious disease, and cancers [7].

Over the past two decades, the overprescription of opioid pain relievers, the availability of heroin, and the increase of synthetic opioids such as fentanyl have given rise to a growing opioid epidemic crisis in the United States, leading to a nationwide public health emergency declaration on October 27th, 2017 [8]. The CDC reported that the number of overdose deaths involving any opioid has increased from 21,089 deaths in 2010 to 81,086 deaths in 2022 with an alarming increase in the number of overdose deaths involving just synthetic opioids from 1.0 death per 100,000 standard person in 2013 to 22.7 in 2022 [9,10]. In addition, OUD along with opioid-related overdose deaths pose a significant economic burden, costing the United States an estimated 1.02 trillion dollars in 2017 [11].

Table 1. FDA-approved pharmacotherapies for the treatment of SUD's.

Substance	Pharmacotherapy	Mechanism of action [16]
Alcohol	Disulfiram	Aldehyde dehydrogenase inhibitor
	Acamprosate	Functional N-methyl-D-aspartate (NMDA) receptor antagonist at high concentrations and agonist at low concentrations
	Naltrexone	Opioid antagonist
Opioid	Methadone	Full opioid agonist
	Buprenorphine	Partial opioid agonist
	Naltrexone	Opioid antagonist
Stimulants	None	None

SUD, substance use disorder.

StUD, driven by substances such as cocaine and methamphetamine, remains without any FDA-approved pharmacological treatment. Globally, there has been an unprecedented surge in the production of stimulants with estimates that 19 million people were users of cocaine in 2018 [3,12]. Multiple studies have highlighted the detrimental impact that stimulant use has on the population, ranging from adverse health effects such as the transmission of infectious diseases, and cardiovascular and respiratory complications to societal disruption such as rising rates of violence, homelessness, and drug dealing [13–15].

Traditional pharmacological treatments for the SUDs of interest to us (Table 1, Ref. [16]) have provided some relief but are often limited by efficacy, side effects, and accessibility. Given these limitations, there is a critical need for novel therapeutics that target the underlying neurobiological mechanisms of addiction more effectively.

This review explores three promising classes of novel therapeutics: corticotropin-releasing factor (CRF) antagonists, glucagon-like peptide-1 (GLP-1) receptor agonists, and dopamine D3 receptor (D3R) antagonists. These therapies have been selected due to their rising popularity, preclinical evidence, and early clinical promise in treating multiple SUDs. Collectively, they target different aspects of the addiction process, such as stress and relapse prevention, reward modulation, and the reduction of drug-seeking behavior, leading to a combined multifaceted approach to treating SUDs [17–19]. This review aims to provide a comprehensive overview of their potential to address the unmet needs in SUD treatment by examining the evidence supporting these treatments and their mechanisms of action (Table 2, Ref. [20–29,34–65]).

2. GLP-1 Receptor Agonists

GLP-1 is an incretin hormone produced in the pancreas and intestinal L-cells in response to food ingestion. It is crucial for regulating glucose levels by enhancing insulin secretion from the pancreas, inhibiting glucagon release, slowing gastric emptying, and reducing appetite [66]. In addition to its glucoregulatory effects, GLP -1 has been proven to decrease both physiologic and pleasure-driven feeding making it a key component in the treatment of type 2 diabetes mellitus (T2DM) and obesity since being approved by the FDA for use in T2DM in 2005 and for obesity in 2014 [67,68].

There are several types of GLP-1 receptor agonists, all mimicking the actions of endogenous GLP-1. The first GLP-1 receptor agonist that was approved by the FDA is Exenatide (marketed as Byetta). It is derived from Exendin-4, a peptide found in the saliva of the Gila monster, and has a shorter half-life, requiring twice-daily injections [66,69]. Liraglutide (marketed as Victoza) on the other hand is a longer-acting GLP-1 receptor agonist, allowing for once-daily injections due to its fatty acid side chain that binds to albumin, prolonging its action in the bloodstream [66,69]. Other GLP-1 receptor agonists include dulaglutide (Trulicity), which is a once-weekly injection due to its long half-life, and semaglutide (Ozempic), which is also administered weekly and has shown superior efficacy in glycemic control and weight loss compared to other GLP-1 receptor agonists [69]. Additionally, there is lixisenatide (Adlyxin), which, like exenatide, requires more frequent dosing but has a slightly different structure, impacting its duration of action and side effect profile [66].

GLP-1 receptors are widely expressed in the brain in regions such as the nucleus accumbens (NAc) and the ventral tegmental area (VTA), which are heavily associated with reward and addiction [70]. By modulating dopamine pathways, these receptors have a critical role in the development and regulation of addiction [71]. The GLP-1 receptors in the VTA and NAc are particularly important because these regions are central to the brain's reward system, the mesolimbic dopamine system. When GLP-1 receptors are activated, they can dampen the rewarding effects of addictive substances by altering dopamine release. Specifically, activating these receptors reduces the activity of dopamine-producing neurons, leading to less dopamine release in the NAc. This decrease in dopamine can lessen the reinforcing effects of drugs, reducing the motivation to use them [72].

2.1 GLP-1 Receptor Agonists for AUD

Several preclinical studies have demonstrated the efficacy of GLP-1 receptor agonists in reducing drug-seeking

Table 2. A summary of preclinical and clinical findings of emerging therapeutics for SUD's.

Medication	Mechanism of action	SUD	Preclinical findings	Clinical findings
Exendin-4	GLP-1 receptor agonist	AUD	↓ relapse-like drinking behavior, ethanol self-administration, CPP, alcohol intake [20–24].	↓ intake, risk of alcohol-related events, incidence and recurrence of AUD in obese patients (body mass index (BMI) >30).
Liraglutide GEP44* Semaglutide				↓ risk of first-time and recurrent AUD diagnosis in type 2 DM patients. ↓ alcohol intake, AUDIT scores, binge-drinking odds, incidence and recurrence of AUD in obese patients (BMI >30) [25–29].
Tirzepatide*		OUD	↓ oxycodone and fentanyl self-administration and reinstatement of seeking behavior [34,35].	
Dulaglutide		StUD	↓ cocaine self-administration, seeking-behavior and CPP [36–38].	no significant differences in the self-administration of cocaine [39].
SB-277011-A R-VK4-116	D3R antagonist	AUD	↓ alcohol intake, seeking behavior, relapse-like drinking, cue-induced ethanol-seeking behavior [40–42].	
BP 897* Pramipexole* R-VK4-40 CAB2-015*		OUD	↓ withdrawal symptoms and tolerance to morphine. Enhanced analgesic effects of oxycodone. ↓ oxycodone intake, self-administration and relapse-seeking behavior. Attenuation of naloxone precipitated CPA [43–45].	
PG01037* PF-4363467* GSK598890		StUD	↓ cocaine seeking behavior and relapse-associated anxiety. ↓ rewarding effects of methamphetamine [46].	
CP-154,526 Antalarmin	CRF1 antagonist	AUD	↓ alcohol intake, self-administration, binge-like alcohol consumption, stress-induced relapse-like drinking, withdrawal symptoms and seeking behavior [47–49]	no significant effect on risk of relapse, stress induced alcohol craving emotional responses or anxiety [50,51].
Urocortin 3* α-helical-CRF		OUD	↓ stress-induced reinstatement of heroin and opioid-seeking behavior and relapse. ↓ withdrawal symptoms and CPA [52–60].	↓ withdrawal symptoms [61].
Pexacerfont Verucerfont		StUD	↓ stress-induced reinstatement of methamphetamine-seeking behavior. ↓ binge cocaine consumption. Prevents and reverses increased cocaine intake induced by social defeat stress [62–65].	↓ cravings, temptation severity and frequency, anxiety and depressive symptoms and an improvement in specific opiate and amphetamine withdrawal symptoms [61].

* Has additional mechanisms of action. ↓ , represent a decrease. GLP-1, glucagon-like peptide-1; D3R, dopamine D3 receptor; CRF, corticotropin-releasing factor; AUD, alcohol use disorder; OUD, opioid use disorder; StUD, stimulant use disorder; DM, diabetes mellitus; AUDIT, Alcohol Use Disorders Identification Test; CPP, conditioned place preference; CPA, conditioned place aversion.

behavior. For instance, one study investigated the impact that the GLP-1 receptor agonist Exendin-4 would have on relapse-like drinking behavior in male C57BL/6NTac mice. These mice are a specific inbred strain of lab mice that were then socially housed, better mimicking human social drinking environments. The mice had continuous access to alcohol for 37 days, which was followed by a period of alcohol deprivation and then the reintroduction of alcohol. During the deprivation and reintroduction of alcohol periods, the mice were subcutaneously administered either 1.5 µg/kg/day of Exendin-4 or saline. The study revealed that Exendin-4 treated mice did not show the significant increase in alcohol intake seen in control mice upon reintroduction after deprivation, suggesting the role that Exendin-4 could have in maintaining long-term abstinence in alcohol use disorder [20].

A similar study was done in which male C57BL/6J mice were intraperitoneally administered with either 1.8 or 3.2 µg/kg of Exendin-4 to investigate its effects on ethanol self-administration. The mice that were pretreated with 3.2 µg/kg of Exendin-4 had a reduction in the amount of self-administered ethanol by at least 70%, compared to their baseline intake. Importantly, Exendin-4's effects on ethanol self-administration were not due to general reductions in motivation or motor function as there was no effect on the operant response for a palatable liquid food [21].

A study on another type of GLP-1 receptor agonist, liraglutide, demonstrated its efficacy in reducing alcohol-induced dopamine release and conditioned place preference in rodents. Alcohol-induced dopamine release in the NAc of mice was significantly attenuated after the acute administration of 0.1 mg/kg of liraglutide. In addition, there was a consistent reduction in alcohol intake and preference when liraglutide was repeatedly administered over eight days and reduced lever responses for alcohol in alcohol-preferring rats under a progressive ratio schedule, indicating reduced motivation to obtain alcohol [22].

The effects on alcohol intake and operant response to palatable food in rats when Exendin-4 was administered in different regions of the brain were investigated. Exendin-4 was injected into the VTA, NAc core and shell, dorsomedial hippocampus, lateral hypothalamus, arcuate nucleus, paraventricular nucleus, and basolateral amygdala. The results showed that the administration of Exendin-4 into the VTA, NAc core and shell, dorsomedial hippocampus, lateral hypothalamus, and basolateral amygdala significantly reduced alcohol intake. However, injections into the arcuate nucleus and paraventricular nucleus did not affect alcohol intake. These findings suggest that GLP-1 receptor signaling in these specific brain regions plays a crucial role in modulating alcohol consumption and reward-driven behaviors [23].

Complementing these findings, a significant reduction in alcohol self-administration in high alcohol drinkers with no impact on food intake or locomotor activity was demonstrated with the administration of Exendin-4 in the VTA in male Long-Evans rats. However, Exendin-4 did not affect the reacquisition of alcohol self-administration after extinction or the motivation to obtain alcohol under a progressive ratio schedule [24].

In humans, a two-part study was conducted, analyzing over 68,000 posts related to GLP-1 receptor agonists on Reddit, a social media platform, and a remote study on 153 obese participants (body mass index (BMI) $\geq$30) who self-reported consuming alcohol and taking either semaglutide, tirzepatide, a dual GLP-1/gastric inhibitory polypeptide agonist, or no weight loss/diabetes medication. Using machine-learning algorithms, 1580 alcohol-related posts were analyzed, with 71% of the posts showing a reduction in alcohol cravings, decreased desire to drink, or other negative effects related to alcohol use while taking a GLP-1 receptor agonist. The remote study revealed that participants on either semaglutide or tirzepatide had a significant reduction in their alcohol consumption, drinks per drinking day, binge-drinking odds, and Alcohol Use Disorders Identification Test (AUDIT) scores [25].

In a predefined secondary analysis of a RCT, alcohol consumption was measured in 151 participants who reported alcohol consumption at baseline and received either dulaglutide (GLP-1 receptor agonist) or a placebo for 12 weeks. While the primary goal of this study was to study the effect of dulaglutide on smoking cessation, which yielded negative results, the dulaglutide group reported a 29% reduction in alcohol consumption compared to the placebo group at the end of the 12 weeks, with greater reductions when adjusting the models to include factors like education. Notably, alcohol consumption did not change among heavy drinkers based on the treatment received, and there was no correlation between changes in smoking and alcohol consumption [26].

Epidemiologic studies have demonstrated the benefits of GLP-1 receptor agonists for AUD. A nationwide cohort study and self-controlled case series in Denmark examined alcohol-related events in 38,454 new users of GLP-1 receptor agonists in comparison to 49,000 users of dipeptidyl peptidase-4 (DPP-4) inhibitors. Individuals initiating GLP-1 receptor agonists had a 46% lower risk of experiencing an alcohol-related event during the first 3 months of treatment and had a 38% reduced risk of alcohol-related events 1 year after GLP-1 treatment when compared to individuals initiating and taking DPP-4 inhibitors within the same time periods. Comparisons were made with the antidiabetic drug, DPP-4 inhibitors, to limit confounding [27]. Another recent study found that semaglutide was associated with a 50–56% reduced risk of both the incidence and recurrence of AUD in obese patients when compared to other anti-obesity medications. In patients with type 2 diabetes mellitus (DM), semaglutide had a 44% reduced risk first-time AUD diagnosis and a 39% reduced risk of recurrent AUD compared to non-GLP1 receptor agonist anti-diabetes medications [28].

A clinical study explored whether Exenatide could help reduce alcohol consumption in patients with alcohol use disorder. This study was randomized, double-blinded, and placebo-controlled, involving 127 patients seeking treatment for alcohol use disorder. Participants were either given 2 mg of subcutaneous Exenatide or a placebo once a week for 26 weeks, along with standard cognitive-behavioral therapy. The study revealed that there was no significant reduction in the number of heavy drinking days between the Exenatide and placebo groups. However, when the patients were divided into subgroups according to their BMI, obese patients with a BMI >30, exenatide significantly reduced the number of heavy drinking days and total alcohol intake. Conversely, in patients with a BMI under 25, exenatide increased the number of heavy drinking days compared to the placebo. Nevertheless, the group receiving Exenatide did have a significant reduction in their alcohol cue reactivity in the ventral striatum and septal area which are key regions for drug reward addiction in addition to lowered dopamine transporter availability in the striatum [29]. There are currently a few ongoing RCTs that are testing the use of semaglutide in individuals with AUD (NCT05895643, NCT05520775, NCT05891587, NCT06015893) [30–33].

2.2 GLP-1 Receptor Agonists for OUD

Exendin-4 is the GLP-1 receptor agonist, that has been most studied for its effects on opioid use. In one study, it was found to significantly reduce oxycodone self-administration and reinstatement of oxycodone-seeking behavior without affecting the analgesic properties of oxycodone. When administered systemically, Exendin-4 was able to cross the blood-brain barrier, binding to GLP-1 receptors on medium spiny neurons in the NAc shell that express dopamine D1 and D2 receptors. As with systemic administration, direct infusion of Exendin-4 into the NAc shell also reduced oxycodone self-administration and reinstatement of oxycodone-seeking behavior, without impacting normal food intake [34].

In contrast, a study found that Exendin-4 did not attenuate the rewarding or reinforcing effects of opioids, as measured by morphine-conditioned place preference (CPP) and intravenous self-administration of remifentanil [73]. Additionally, Exendin-4 did not affect morphine withdrawal symptoms or analgesia, indicating that GLP-1 receptor agonists might not be effective in reducing opioid addiction-related behaviors in all contexts.

To address the limitations of single GLP-1 receptor agonists, a study explored the effects of the dual agonist GEP44 on fentanyl use behaviors. GEP44 significantly reduced fentanyl self-administration and seeking without the adverse effects seen with Exendin-4, such as nausea and reduced food intake. This study suggests that dual agonists targeting both GLP-1 and neuropeptide Y2 receptors may offer a more effective and tolerable treatment for OUD [35].

There have also been multiple studies that focused on the role of specific neural pathways in opioid reinforcement and relapse. Researchers demonstrated that context-induced reinstatement of heroin seeking was associated with increased activation of ventral subiculum neurons projecting to the NAc shell. Disrupting this pathway significantly decreased context-induced reinstatement, highlighting the ventral subiculum to NAc shell pathway's critical role in relapse mechanisms and suggesting potential targets for interventions [74].

In addition, researchers found that heroin increases dopamine levels in the NAc by activating a subset of dopamine neurons in the medial VTA that project to the medial NAc shell. Inhibiting these neurons significantly decreased heroin self-administration, highlighting the importance of the dopamine pathway in opioid reinforcement and suggesting potential targets for therapeutic interventions [75].

2.3 GLP-1 Receptor Agonists for StUD

A study found that direct administration of 0.05 µg of the GLP-1 receptor agonist Exendin-4 into the VTA of rats significantly reduced cocaine self-administration [36]. It, however, did not affect the self-administration of sucrose, supporting a previous study that showed that intra-VTA infusions of a similar dose of Exendin-4 do not induce any locomotor impairment or malaise, thus any reduction in cocaine intake was not due to drug-induced motor impairments [36,76]. Multiple studies have corroborated these findings when the same dose of 0.05 µg Exendin-4 is injected directly into the VTA, NAc core, and shell resulting in significant attenuation of cocaine-seeking behavior in rats with no effect on sucrose-seeking behavior [77]. This was also seen with a dose of 0.025 µg injected directly into the laterodorsal tegmental nucleus of rats [72,78].

Adding to these findings, a recent study used chemogenetic activation in rats to stimulate GLP-1-producing neurons in the nucleus tractus solitarius (NTS) that project to the VTA, in which plasma GLP-1 levels decreased after voluntary cocaine use. These GLP-1 neurons were found to be primarily located on γ-aminobutyric acid (GABA) neurons in the VTA and not on dopamine neurons, and their activation led to reduced cocaine-seeking behavior during abstinence. Reduced cocaine-seeking behavior was also seen when exendin-4 was administered [37].

Furthermore, the study highlighted a potential mechanism in which GLP-1 signaling might help reduce the reinforcing effects of cocaine. This is as the administration of cocaine activated the GLP-1 neurons in the NTS which sends signals to the VTA, a crucial part of the brain's reward system, playing a major role in addiction. The activation of GLP-1 neurons in the NTS also increased the plasma corticosterone levels, a stress hormone, suggesting that the activation of GLP-1 neurons is a protective mechanism in the body's stress response to counteract the reinforcing ef-

fects of cocaine. This was supported by microinjecting corticosterone directly into the hindbrain's fourth ventricle, resulting in a reduction in cocaine self-administration and a blockage of this effect by pretreatment with a GLP-1 receptor antagonist in the VTA [36].

When mice were pretreated with Exendin-4 at doses of 10, 30, or 100 µg/kg, cocaine-CPP was significantly reduced with no effect on cocaine-induced locomotion, indicating that Exendin-4 caused a reduction in CPP that was not due to a decrease in activity but by attenuating the rewarding effects of cocaine [38]. The effects of Exendin-4 on cocaine-induced locomotion were not consistent, as the acute and repeated administration of Exendin-4 at a lower dose of 2.4 µg/kg caused a reduction in both cocaine and amphetamine-induced locomotion, along with dopamine release in the NAc [79]. This was also seen when a dose of 30 µg/kg of Exendin-4 was administered, reducing amphetamine-induced hyperlocomotion, suggesting that doses of Exendin-4 can have varying effects on stimulant-induced locomotion of drugs like cocaine and amphetamine [80].

Few clinical studies have investigated the use of GLP-1 receptor agonists in people with StUD. An experimental study revealed decreased serum concentrations of GLP-1 in eight experienced cocaine users after receiving 25 mg of intravenous therapy (IV) cocaine. The administration of 5 µg of exenatide to 13 participants with cocaine use disorder reported no significant differences in the self-administration of cocaine or subjective effects [39]. A case series of three patients with cocaine use disorder who were treated with 2 mg of extended-release exenatide for 6 weeks yielded mixed results but was well tolerated with no severe adverse effects. Exenatide had no effect on two patients that continued their cocaine use but led to abstinence in one patient in the last two weeks of treatment [81]. Similar to the previous study, an ongoing clinical trial is investigating the use of extended release exenatide for 6 weeks on patients with cocaine use disorder (NCT06252623) [82].

2.4 Summary—GLP-1 Receptor Agonists

The use of GLP-1 receptor agonists as a therapeutic for AUD, OUD, and StUD has shown some promising results, although there have been some varying outcomes based on the setting in which it is used. In AUD, preclinical studies have demonstrated that GLP-1 receptor agonists like Exendin-4 and liraglutide have been effective in reducing alcohol intake and the motivation to obtain alcohol, with effects dependent on specific brain regions and conditions, such as BMI in clinical trials. Social media analysis has demonstrated reduced alcohol cravings and consumption in individuals taking GLP-1 receptor agonists, and clinical trials have shown similar reductions in alcohol consumption seen in obese patients taking dulaglutide or semaglutide. For OUD, Exendin-4 has been found to reduce oxycodone self-administration and relapse, however, its effectiveness has not been consistent across all types of opioids. In addition, the use of dual agonists shows potential in reducing opioid use with fewer side effects. In StUD, Exendin-4 has been effective in decreasing cocaine self-administration and CPP without impacting general motivation or locomotion, however, in humans, exenatide showed no significant differences in the self-administration of cocaine. Further research is needed to fully understand the therapeutic potential of GLP-1 receptor agonists in SUDs and to address limitations such as variability in effectiveness across different substances, dosages, and administration methods.

3. D3R Antagonists

The VTA and the NAc are pathways in the mesolimbic dopamine system that play an important role in the rewarding and reinforcing properties of drugs. Dopamine D3Rs, being highly expressed in these limbic regions, have been implicated in the development of addiction and drug-seeking behavior. Increased receptor expression is a form of neuroadaptation resulting from chronic use of substances which contributes to the hypodopaminergic state associated with drug cravings and relapse. Selective dopamine D3R antagonists have the potential to be a novel therapeutic strategy for SUD by normalizing dopamine signaling and diminishing the reinforcing properties of drugs [83–85].

3.1 D3R Antagonists for AUD

Several preclinical studies have investigated the role of the dopamine D3R in AUD yielding promising results on the ability of D3 antagonists to reduce the consumption of alcohol and mitigate relapse behaviors in rats [40,41]. For example, the use of SB-277011-A, a highly selective D3R antagonist, had an acute and dose-dependent reduction in both the intake and seeking behavior of alcohol in ethanol-preferring and non-preferring rats though to a slightly lesser degree in the latter [42]. A similar study using SB-277011-A and BP 897, a partial agonist, revealed a dose-dependent reduction in both relapse-like drinking and cue-induced ethanol-seeking behavior [84]. In addition, the upregulation of striatal D3R with chronic alcohol consumption was found to be true regardless of genetic predispositions to alcohol preference, as confirmed by quantitative reverse transcription polymerase chain reaction (qRT-PCR) [84].

While there are substantial preclinical studies with strong evidence for the role of D3R antagonists for AUD, the literature on human studies is limited. A preclinical study suggested that D3R antagonists given at high doses may be better at managing AUD compared to naltrexone and acamprosate, which are established treatments [86]. A first-of-its-kind study was done in humans which compared the availability of dopamine D3R between 16 male subjects with a diagnosis of alcohol dependence meeting the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria that had been abstinent for at least four weeks and 13 healthy male controls [87]. Positron emis-

sion tomography (PET) with a Dopamine D3R-preferring radioligand was used to scan various brain regions for the availability of the receptor. Contrary to previous preclinical studies, there were no significant differences in the binding of the radioligand in the striatal regions of the subjects, however, there was a higher binding of the radioligand in the hypothalamus of the alcohol-dependent subjects compared to healthy controls. This was further validated by a recent study which used a similar methodology to compare the regulation of dopamine D3Rs in subjects with early abstinence AUD and healthy controls [88]. The study revealed that compared to healthy controls, there was a significant decrease of dopamine D3R levels in all regions of the brain with markedly decreased levels in the striatum and no evidence of increased dopamine D3R levels in subjects with AUD.

3.2 D3R Antagonists for OUD

Given the critical role that dopamine D3Rs have in drug-seeking behavior and addiction, the use of D3 antagonists is a logical therapeutic approach. One study showed that the use of pramipexole, a dopamine D3R agonist, alongside morphine in mice and rats maintained analgesia and significantly reduced withdrawal symptoms compared to morphine alone [43]. This showed that the chronic administration of morphine alone resulted in decreased analgesia which indicated the development of tolerance, as opposed to a combination therapy which prevented this tolerance and mitigated withdrawal symptoms, suggesting a potential therapeutic strategy for long-term opioid therapy in chronic pain management.

Interestingly enough, a study in rats and mice in which R-VK4-40, a highly selective dopamine D3R antagonist was used, did not compromise the analgesic effects of oxycodone when co-administered, instead it enhanced its effects [44]. In addition, in the self-administration tests, there was a dose-dependent inhibition of oxycodone intake and lowered break-points for oxycodone self-administration under progressive ratio reinforcement, when pretreated with R-VK4-40. This indicates that R-VK4-40 was able to decrease the maximum effort that the rodents were willing to exert to obtain a dose of oxycodone effectively lowering the motivation to obtain oxycodone.

Numerous studies have supported the efficacy of dopamine D3R antagonists in reducing opioid self-administration and preventing relapse. The use of VK4-116, another selective dopamine D3R antagonist, revealed a dose-dependent inhibition in the acquisition and maintenance of oxycodone self-administration and inhibition of oxycodone-seeking behavior when pretreated with VK4-116, demonstrating its ability to reduce drug-seeking during withdrawal. VK4-116 lowered the break-point for oxycodone self-administration under progressive-ratio reinforcement and shifted the oxycodone dose-response curve downward. When a small dose of VK4-116 was injected after a period of abstinence, there was no reinstatement of the seeking behaviors for oxycodone, indicating its potential to prevent relapse. In addition, VK4-116 did not compromise oxycodone's antinociceptive effects and instead, enhanced oxycodone-induced analgesia, while also attenuating naloxone-precipitated conditioned place aversion in rats chronically treated with oxycodone. It should be noted that the effects of VK4-116 were specific to drug addiction and not other reward-seeking behaviors since it did not affect the self-administration of sucrose. On the other hand, a study on CAB2-015, a novel dopamine D3R antagonist/partial agonist revealed that along with its effects on drug addiction, it also reduced oral sucrose self-administration, suggesting potential effects on natural rewards [45]. A similar study showed that VK4-116 decreases the self-administration of oxycodone and reduces hyperalgesia and irritable behaviors associated with withdrawal in rats [89].

A study on the safety profile of the selective dopamine D3R antagonist PG01037 revealed a dose-dependent attenuation of morphine-induced hyperactivity at doses that did not affect basal locomotion while significantly reducing locomotor activity when 1 and 10 mg/kg of PG01037 was administered following 18 and 56 mg/kg of morphine. However, PG01037 could not prevent locomotor sensitization when repeated doses of morphine were administered, with the mice eventually having a similar response to vehicle-treated mice. While PG01037 alone did not disrupt thermal nociception, contrary to newer dopamine D3R antagonists like VK4-116 and R-VK4-40, there was a dose-dependent attenuation of the antinociceptive effects of morphine by 40% and 54% at 1 and 10 mg/kg, respectively, when pretreated with PG01037. Importantly, there was no catalepsy with the administration of PG01037 alone or in combination with morphine [83]. The selective dopamine D3/D2 receptor antagonist PF-4363467, also attenuated opioid self-administration and drug-seeking behavior without any side effects associated with D2 receptors like catalepsy or extrapyramidal symptoms [90].

3.3 D3 Antagonists for StUD

It has been well established the extent to which both the mesolimbic and nigrostriatal dopamine pathways play a role in StUD, with varying mechanisms for each stimulant [91]. Amphetamines and methamphetamines have been found to reverse vesicular monoamine transporter 2, resulting in the release of dopamine into the extracellular space by reversal of membrane dopamine transporter. Cocaine also increases extracellular levels of dopamine but by blocking dopamine reuptake [92–94]. The elevated levels of dopamine in the extracellular space that occur as a result of these stimulants have been linked to feelings of euphoria [95]. As a result, an effective treatment for StUD would be either to block dopamine receptors, or target dopamine transporters [96].

The role that D3Rs play in stimulant addiction is demonstrated by the chronic administration of methamphetamine to D3R mutant mice leading to weakened behavioral sensitization to methamphetamine and changes in the intracellular signaling pathways [46,97]. SB-277011-A is one of the most promising and widely studied D3R antagonists in animal models of stimulant addiction. It has been shown to attenuate methamphetamine-induced locomotor activity and sensitization and reduce cocaine-seeking behavior in rats as assessed by second-order reinforcement, a model that is very similar to human drug cravings triggered by drug-related cues [98,99]. BP-897 is another D3R antagonist that has also shown promising results by decreasing the rewarding effects of methamphetamine in rats [100]. Additionally, it has been shown to both reduce cocaine-seeking behavior and have anxiolytic effects, aiding in stress attenuation for the prevention of relapse [101].

While D3R antagonists have shown potential in preclinical studies, their translation to clinical settings has been difficult. A major concern with many of these D3R antagonists has been their safety profile. GSK598890, a highly selective D3R antagonist, has proven effective in clinical studies in smokers and overweight individuals, alleviating cigarette smoking cravings and food cues [102–104]. However, in animal models administered cocaine, it has been shown to increase blood pressure [105]. Whilst this was also the case for SB-277011A, the development of a newer D3R antagonist such as R-VK4-116 has demonstrated very high metabolic safety [105,106]. R-VK4-116 has exhibited good brain penetration when administered orally and has shown excellent therapeutic utility in OUD [107].

3.4 Summary—D3R Antagonists

In preclinical studies, using D3 antagonists for treating SUDs have revealed some limitations and mixed results across different substances. For the treatment of AUD, SB-277011-A, and BP 897 have demonstrated dose-dependent reductions in alcohol intake and relapse-like behaviors in animal models, though human studies are limited and have conflicting results regarding the availability of D3Rs in alcohol-dependent individuals. The involvement of the receptor for activated C kinase 1 (RACK1)/brain-derived neurotrophic factor (BDNF)/D3R pathway in reinforcing alcohol intake supports the potential use of D3R antagonists in AUD. In OUD, D3 antagonists such as R-VK4-40 and VK4-116 have been effective in reducing opioid self-administration and preventing relapse, whilst other D3 antagonists, like PG01037, have not had the same efficacy. SB-277011-A and BP-897 have been successful in attenuating stimulant-induced behaviors and reducing drug-seeking, though also lack any clinical findings and carry unfavorable adverse effects, limiting their use in humans. The use of R-VK4-116 in SUDs could be promising, but needs to be researched further in the context of StUD. Overall, while D3R antagonists have shown promise in preclinical models, their translation to clinical research comes with manly limitations, including their applicability to human scenarios, since many preclinical models use passive drug administration, limited dose-response evaluations, and acute treatments rather than chronic exposure. In addition, extinction training is commonly used in relapse models, reducing their validity as humans do not undergo extinction in real-life relapse. While abstinence models without extinction can improve validity, other confounding factors such as stress can skew the results [19].

4. CRF Antagonists

CRF plays a significant role in the body's response to stress, and its dysregulation has been implicated in various forms of substance use disorders, including StUD. The CRF system, particularly the CRF1 receptor, is involved in the stress-induced relapse and withdrawal symptoms associated with stimulant addiction.

4.1 CRF Antagonists for AUD

The CRF1 receptor plays a central role in mediating the stress-related aspects of AUD resulting in a significant reduction of ethanol self-administration in ethanol-dependent animals. The systemic administration of a CRF1 antagonist resulted in a decrease in the intake of ethanol in rats that were dependent on ethanol via intermittent ethanol vapor exposure [47]. In non-ethanol-dependent rats, CRF1 antagonists did not exert their effect indicating that CRF1 antagonism is particularly effective in conditions of dependence where the CRF system is hyperactive [47]. Additionally, a different study demonstrated that the CRF1 receptor antagonist antalarmin significantly reduced both the acquisition and maintenance of ethanol consumption in isolation-reared Fawn-Hooded rats [48]. The study suggested that antalarmin's effects were specific to its action on CRF1 receptors and not due to general anxiolytic effects, indicating that CRF1 receptors are integral to reward-related behaviors and could be targeted to reduce volitional ethanol consumption [48].

In drinking in the dark models, mice were induced to consume high levels of ethanol, elevating their blood ethanol concentrations to levels associated with behavioral intoxication. In those mice, the administration of the CRF1 receptor antagonist CP-154,526 resulted in a dose dependent reduction of ethanol consumption when exposed to conditions that promote excessive drinking. The reducing effects of CP-154,526 were more apparent in mice with high levels of consumption, while moderate drinkers were not significantly affected. This is likely due to the role that CRF1 receptor antagonist plays in stress pathways that occur in excessive drinking, resulting in a more prominent effect as the level of ethanol consumption increases [49].

Furthermore, a study found that CRF1 receptor antagonism reduced binge-like alcohol consumption in the DID

model, highlighting the role of CRF signaling in the extended amygdala in promoting excessive alcohol consumption [108].

A later study explored how brief binge ethanol consumption affects CRF receptor signaling in the VTA [109]. The researchers found that binge ethanol intake enhanced CRF1 receptor-mediated potentiation of N-methyl-D-aspartate (NMDA) receptor currents in the ventral tegmental dopamine neurons [109]. The Intra-ventral tegmental administration of CP-154,526 significantly reduced binge ethanol consumption, indicating that CRF1 receptor activity in the VTA is crucial for sustaining high levels of ethanol intake during binge episodes [109].

In an animal model of relapse, intra-median raphe nucleus infusions of CRF reinstated alcohol-seeking behavior in rats previously trained to self-administer alcohol. This effect was blocked by a CRF1 receptor antagonist, further supporting the role of CRF1 in mediating stress-induced relapse. In addition, the use of foot shock stress as a trigger for relapse has shown that CRF1 antagonists can also effectively block the reinstatement of alcohol-seeking behavior [110]. This study was completed two years after a previous study by the same authors that showed that CRF receptor antagonists could significantly attenuate stress-induced relapse, even when corticosterone, a key stress hormone, was removed [111]. The blockage of stress-induced reinstatement of alcohol-seeking behavior in mice by CRF1 receptor antagonists was also found to be true in mice with a history of heavy alcohol consumption [112].

The CRF1 receptor is primarily associated with promoting ethanol intake and stress-related behaviors, however, there is also the CRF2 receptor which appears to play a more complex role. Activation of CRF2 receptors, particularly in the central nucleus of the amygdala, has been shown to reduce ethanol self-administration in ethanol-dependent rats. For example, the administration of Urocortin 3, a selective CRF2 agonist, into the central nucleus of the amygdala significantly decreased ethanol intake in dependent rats. Interestingly though, in nondependent rats, Urocortin 3 had the opposite effect, increasing ethanol self-administration [47].

Further studies have demonstrated that chronic ethanol exposure leads to long-lasting changes in CRF signaling, particularly within the amygdala, a key brain region involved in stress and anxiety. For example, increased CRF immunoreactivity has been observed in the amygdala weeks after withdrawal, indicating that the CRF system remains hyperactive during abstinence and contributes to the sustained anxiety-like state [113]. CRF antagonists, by blocking this hyperactivity, may help to normalize the stress response and reduce the risk of relapse during this vulnerable period [113]. This was further supported by showing that chronic alcohol exposure upregulated CRF1 receptor expression in the amygdala and bed nucleus of the stria terminalis [114]. Upon withdrawal, these regions exhibited heightened sensitivity to CRF, which was linked to increased anxiety-like behavior and alcohol-seeking. Administration of CRF1 receptor antagonists mitigated these withdrawal-induced behaviors, indicating that targeting CRF1 receptors might be effective in managing withdrawal symptoms and reducing relapse risk [114].

Clinical trials testing the effects of CRF1 receptor antagonists in AUDs in humans have been disappointing. A sample of 39 anxious, alcohol-dependent women who no longer needed treatment for alcohol withdrawal and had undetectable breath alcohol concentrations were randomly assigned to 350 mg/day of verucerfont, another CRF1 receptor antagonist, or a placebo for 3 weeks. In this double-blind trial, verucerfont effectively blocked hypothalamic-pituitary-adrenal axis responses as evidenced by lowered adrenocorticotropic hormone and cortisol levels in the dexamethasone CRF test; however, it was unsuccessful in clinically managing the stress or alcohol cue-induced craving, demonstrating no difference in risk of relapse in the participants [50]. The use of a different CRF1 receptor antagonist, pexacerfont, also had no significant effect on stress-induced alcohol craving, emotional responses, or anxiety, despite reaching 90% CRF occupancy in the brain [51].

4.2 CRF Antagonists for OUD

A pivotal study was conducted that explored the role of CRF1 receptors in the basolateral amygdala and extended amygdala in mediating stress-induced relapse to opioid-seeking behavior [52]. The researchers administered the CRF1 receptor antagonist antalarmin systemically and directly into the basolateral amygdala, finding that both methods significantly reduced stress-induced reinstatement of heroin-seeking behavior in rats. This study highlighted the critical involvement of CRF1 receptors in the basolateral amygdala and suggested that targeting these receptors could be a therapeutic strategy to prevent stress-induced relapse in OUD [52].

A similar study investigated the effects of CRF1 receptor antagonism on stress-induced relapse, focusing on the extended amygdala [53]. Using a rat model of heroin addiction, they found that systemic and intra-amygdala administration of antalarmin significantly reduced stress-induced reinstatement of heroin-seeking behavior [53]. These findings reinforce the role of CRF1 receptors in the extended amygdala in mediating stress-induced relapse [53]. This was further supported by demonstrating that the CRF1 receptor antagonist CP-154,526 effectively attenuates stress-induced relapse in heroin-trained rats. An older study in 1998, alongside the works by Gilpin and Papaleo, provides strong evidence for the critical role of CRF1 receptors in stress-induced opioid relapse [52–54].

A slightly different study showed that intracerebroventricular injections of CRF could mimic the effects of stress, reinstating heroin-seeking behavior even after prolonged drug-free periods. This effect was blocked by alpha-

helical CRF, a peptide CRF antagonist, highlighting CRF's critical role in mediating the stress-induced relapse pathway. Interestingly, this CRF-mediated reinstatement was distinct from drug-priming-induced relapse, which was less sensitive to CRF antagonism. This distinction highlights the specific involvement of CRF in stress-related relapse mechanisms as opposed to other forms of relapse [55].

Opioid withdrawal is marked by negative affective states, largely driven by heightened CRF activity in the brain's stress circuits. A 2005 study examined the effects of CRF receptor antagonists, including α-helical CRF (9-41) and antalarmin, on the aversive effects of opioid withdrawal. They found that these antagonists effectively reduced anxiety-like behaviors and conditioned place aversion (CPA) in rats, indicating that CRF plays a crucial role in the negative affective states of opioid withdrawal [56]. Additional insight was provided into the role of CRF in opioid withdrawal, showing that CRF1 receptor antagonists reduce heroin self-administration in rats with extended access to the drug, which mimics the escalation seen in human addiction [57].

A study by Sabino *et al.* [58] focused on the dysphoric states induced by opioid withdrawal and the potential for CRF1 receptor antagonists to alleviate these states. Their findings indicated that CRF1 receptor antagonism significantly reduced withdrawal-induced dysphoria, as evidenced by decreased CPA and reduced stress-induced reinstatement of opioid-seeking behavior. Further study revealed that mice did not exhibit the negative affective symptoms typically associated with opioid withdrawal, such as CPA and increased dynorphin expression in the NAc [59].

The role of CRF2 receptors in opioid withdrawal was investigated using CRF2 receptor knockout mice. The study found that these mice exhibited exacerbated withdrawal symptoms, including heightened anxiety-like behavior and increased corticosterone levels, suggesting that CRF2 receptors play a protective role in modulating the stress response during opioid withdrawal [60].

Clinical application of these findings was done by evaluating the efficacy of pexacerfont, a CRF1 receptor antagonist, in patients undergoing opioid and methamphetamine detoxification. The study found that pexacerfont was effective in reducing withdrawal symptoms, particularly in alleviating anxiety and stress-related symptoms during the early stages of detoxification. However, the long-term benefits of CRF1 antagonism in maintaining abstinence and preventing relapse remain unclear, indicating a need for further research [61].

4.3 CRF Antagonists for StUD

The literature on the use of CRF receptor antagonists for StUDs is limited, focusing mainly on disorders of cocaine use. Regarding its effects on methamphetamine in rats, a study found that levels of CRF in the amygdala and plasma significantly increased during withdrawal from methamphetamine. This was especially evident on particularly on the 10th day, correlating with a heightened anxiety-like behavior observed in the rats. Both the administration of a non-selective CRF antagonist and a selective CRF1 receptor antagonist effectively attenuated the stress-induced reinstatement of methamphetamine-seeking behavior [62].

In mice, blocking of CRF receptor 1 in the VTA has been shown to prevent the development of stress-induced locomotor sensitization and the escalation of cocaine intake during a 24-hour binge session [63]. In addition, it has been demonstrated to both prevent and reverse the escalation of cocaine intake induced by social defeat stress in mice [64]. However, it should be noted that despite the previous findings in rodent models, neither the acute nor chronic administration of antalarmin had a significant effect on cocaine self-administration or discrimination in rhesus monkeys but did induce sedation at higher doses [65]. One clinical study was conducted in male patients with heroin and methamphetamine dependance, assessing the efficacy of pexacerfont in managing withdrawal symptoms. The participants were randomized to receive either pexacerfont or placebo for three weeks. The participants receiving pexacerfont were administered 300 mg/day for the first week, 200 mg/day for the second, and 100 mg/day for the third. Though there were no differences in urine tests for heroin or methamphetamine between the groups, the participants receiving pexacerfont showed better outcomes on different tests and had no adverse effects. Pexacerfont treatment significantly reduced cravings, temptation severity and frequency, anxiety, and depressive symptoms, and led to an improvement in specific opioid and amphetamine withdrawal symptoms [61].

4.4 Summary—CRF Antagonists

CRF antagonists primarily target the stress-related pathways that contribute to relapse and excessive drug use with CRF1 receptor antagonists like CP-154,526 and antalarmin showing good efficacy for the treatment of AUD in preclinical studies. In clinical trials, CRF1 antagonists like verucerfont and pexacerfont have failed to show efficacy in reducing alcohol cravings or preventing relapse in alcohol-dependent individuals. In severe OUD, CRF1 antagonists have been efficacious in reducing stress-induced relapse, mitigating withdrawal symptoms, and decreasing opioid self-administration. Studies also suggest that CRF2 receptors may play a protective role during withdrawal, though more research is needed to clarify their therapeutic potential. In StUD, CRF1 antagonists have shown promise in animal models by preventing stress-induced relapse and reducing drug-seeking behaviors and their effectiveness in clinical trials have been limited, but did show some potential in patients with both OUD and StUD. Human studies have not demonstrated successful results due to a multitude of reasons. Ethical constraints limit the ability to directly test CRF1 antagonists on key addiction-related behaviors

such as escalation of drug use, and animal models often rely on forced abstinence/extinction protocols without accounting for alternative reinforcers, limiting their application to human stress-related drug-seeking behavior. Along with the lack of variability in the populations used in clinical trials, developing models that are more extensive and tailored to specific subpopulations could lead to new advancements in the use of CRF1 antagonists in human addiction [18,115].

5. Conclusions

SUDs pose a massive public health and economic burden on society, demanding more effective and disseminated treatments. This review exhibited promising findings for the use of novel therapeutics such as GLP-1 receptor agonists, D3R antagonists, and CRF antagonists in addressing AUD, OUD, and StUDs. Nevertheless, further research should explore the use of CRF antagonists in specific subpopulations, such as those with high stress or comorbid anxiety, to better assess their potential in stress-driven relapse prevention. The use of newly designed animal models to include voluntary abstinence and chronic treatment protocols can also help in developing more effective interventions in humans. GLP-1 receptor agonists have shown promise, especially in AUD and OUD. Further research into their role in reducing drug-related dopamine release and cravings, along with the use of dual agonists such as GEP44, could lead to greater efficacy in treating SUDs. Further trials are needed to test the efficacy of D3R antagonists in humans, however, their ability to reduce drug-seeking behaviors without affecting natural rewards or motor function can be valuable in StUD. Preclinical models focusing on prolonged treatment with D3R antagonists and the combination with other receptor-specific treatments can enhance their clinical use, especially in poly-substance dependance. In summary, novel therapeutics targeting CRF, GLP-1 and D3 receptors show promise for advancing the treatment of SUD's.

Author Contributions

Conceptualization and overview by KD and BF. Section writing and graphical abstract design by KD. Editing by KD and BF. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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The authors declare no conflict of interest.

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