HHS Public Access

Author manuscript

Pharmacol Biochem Behav. Author manuscript; available in PMC 2025 May 15.

Published in final edited form as:

Pharmacol Biochem Behav. 2025 March ; 248: 173952. doi:10.1016/j.pbb.2024.173952.

Emerging medications and pharmacological treatment approaches for substance use disorders☆

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Abstract

Medications to treat substance use disorders (SUDs) remain suboptimal or, in the case of stimulants and cannabis, non-existent. Many factors have contributed to this paucity, including the biological complexity of addiction, regulatory challenges, and a historical lack of enthusiasm among pharmaceutical companies to commit resources to this disease space. Despite these headwinds, the recent opioid crisis has highlighted the devastating consequences of SUDs for both individuals and society, stimulating urgent efforts to identify novel treatment approaches. In addition, several neurobiological systems have been recently implicated in unique aspects of drug reward, opening the door to candidate medications with novel mechanisms of action. Here, we provide an overview of efforts to target several of these new systems, with a focus on those that are the subject of ongoing clinical trials as well as being areas of interest among the authors' research groups (MHJ, MTB, NAE). Specifically, we discuss new classes of medications targeting the serotonin 2A receptor (i.e., psychedelics), glucagon-like peptide 1 receptor, cannabidiol, dynorphin/kappa opioid receptor, orexin/hypocretin, and oxytocin receptor systems, as well as emergent approaches for modulating the more canonical dopaminergic system via agonist therapies for stimulant use disorders. Collectively, innovations in this space give reason for optimism for an improved therapeutic landscape for substance use disorders in the near future.

☆For submission as a review article as part of the *Pharmacology, Biochemistry and Behavior* 50th Anniversary Special Issue (Editors Stoops and Moore).

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1. Introduction

Substance use disorders (SUDs) constitute a substantial public health issue, impacting the lives of millions of individuals and imposing substantial economic and social challenges on communities worldwide (Degenhardt et al., 2018). The recent opioid epidemic, characterized by mounting rates of opioid-related overdose deaths and addiction, has illuminated the dire need for effective interventions. The complexity of SUDs extends beyond individual health, as these disorders contribute to increased healthcare costs, criminal justice involvement, and lost productivity, further underscoring the necessity of innovative treatment solutions.

Despite increased precision in our understanding of the neurobiology of SUDs over recent years, the available pharmacological treatments for SUDs have remained scant (Volkow, 2020). Currently, the U.S. Food and Drug Administration (FDA) has approved only a limited number of medications to treat opioid use disorder (OUD), nicotine use disorder (NUD), and alcohol use disorder (AUD). Pharmacological treatments for OUD and NUD typically involve a form of agonist therapy; the use of agonists or partial agonists with lower addictive potential and better safety profiles (i.e., slower entry into the brain and longer duration of action) to dampen the reward- and withdrawal-related consequences of more addictive agonists of the same receptor systems (Jordan et al., 2019). For OUD, this often involves medications such as methadone (μ-opioid receptor agonist) and/or buprenorphine (μ-opioid receptor partial agonist), and for NUD, this can involve nicotine patches/gums (nicotinic acetylcholine receptor agonist) or varenicline ($\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist). Pharmacological treatments for AUD include acamprosate (NMDA antagonist and $GABA_A$ allosteric modulator), which acts to attenuate the severity of alcohol withdrawal and reduce craving (Marin et al., 2023), and naltrexone (opioid receptor antagonist), which dampens the euphoric effects of alcohol consumption induced by endogenous opioids. Despite their demonstrated efficacy in reducing SUD-related morbidity and mortalities (Wakeman et al., 2020), substantial proportions of individuals undergoing these agonist therapies for OUD and NUD still experience relapse/return to use (Bell and Strang, 2020; Schnoll et al., 2015), and treatments for AUD demonstrate only modest efficacy (Jonas et al., 2014).

Critically, at present, no FDA-approved medications currently exist for the treatment of stimulant use disorders (StUDs), inhalant use disorders, and cannabis use disorder (CaUD) (Jordan et al., 2019). Consequently, in the case of StUDs [e.g., cocaine use disorder (CoUD) and methamphetamine use disorder (MUD)], the standard frontline treatments are psychosocial interventions such as cognitive behavioral therapy (CBT) and contingency management. However, the effectiveness of these interventions is limited by various factors (Farrell et al., 2019; Ronsley et al., 2020). CBT is a therapist-delivered psychological intervention targeted at helping individuals identify cues (i.e., environments, thoughts, feelings, and circumstances) that predict substance use and develop coping skills and strategies (Sofuoglu et al., 2016). Despite its frontline status, meta-analytic evidence indicates that CBT does not significantly improve abstinence from stimulant use compared to usual care (Farrell et al., 2019; De Crescenzo et al., 2018; Minozzi et al., 2024), and demonstrates high levels of attrition (i.e., 70% at 12 weeks) (Smout

et al., 2010; Lappan et al., 2020). Moreover, although the strongest evidence supports the efficacy of contingency management compared to other interventions (Brown and DeFulio, 2020; Bentzley et al., 2021; Kampman, 2019)—a behavioral intervention wherein individuals are positively reinforced (financially or non-financially) for reducing and/or abstaining from substance use for target durations—for improving StUD outcomes, these interventions are rarely conducted and not widely accessible (Ronsley et al., 2020). This reluctance toward implementing contingency management programs is likely due to high financial costs, lack of clinical education about implementing programs, loss of abstinence-promoting effects once reinforcement is removed, as well as ideological opposition and stigma toward this form of treatment (Kampman, 2019; Kirby et al., 2006; Rawson et al., 2023). Notably, meta-analytic evidence indicates that combining contingency management with (experimental) pharmacological treatments for StUDs can produce superior efficacy compared to contingency management or pharmacological treatment alone (Tardelli et al., 2018). Notably, however, the pharmacological compounds used in these studies have failed to gain regulatory approval for use in StUD populations, highlighting the need for further efforts to develop adjunctive treatment approaches (Abuse, 2020).

In this review, we offer an overview of the current state of various efforts to develop treatments for SUDs, with an emphasis on those that are currently the subject of ongoing clinical trials, as well as a focus on ongoing work in our research groups (MHJ, MTB, and NAE). Firstly, we discuss efforts to develop agonist therapy strategies for StUDs – an endeavor that has been ongoing for over two decades but has gained recent traction in clinical trials. Next, we provide an overview of neural systems that have been implicated in SUDs, and for which medications have been developed for alternative indications, making their potential repurposing (or optimization of related compounds for use in SUD populations) theoretically straightforward. Specifically, we focus on compounds that target the serotonin 2A receptor (i.e., psychedelics), glucagon-like peptide 1 receptor (GLP-1R), cannabidiol, oxytocin, orexin-hypocretin, and dynorphin/kappa opioid receptor systems. For a summary of the pharmacological treatments for SUDs discussed in this review, refer to Table 1.

2. Psychostimulant-based agonist therapy for stimulant use disorders.

The rationale behind psychostimulant-based treatments for StUDs mirrors the rationale of agonist therapies for opioid use disorder and nicotine use disorder (as described in the Introduction) (Herin et al., 2010; Grabowski et al., 2001). Both cocaine and methamphetamine functionally elevate intrasynaptic levels of dopamine and other monoamines, albeit via different mechanisms: cocaine blocks the reuptake of dopamine via inhibition of the dopamine transporter (DAT), whereas methamphetamine both blocks dopamine reuptake and stimulates further presynaptic monoaminergic release (Ciccarone, 2011; Strzelecki et al., 2022). Furthermore, evidence from post-mortem human studies demonstrates that chronic stimulant use results in dopaminergic system dysfunction, including altered striatal DAT and dopamine D2 and D3 receptor availability (Kohno et al., 2022). Thus, modulation of dopaminergic systems via regulated, ‘safer’ psychostimulants potentially represents a logical treatment approach for StUDs (Tardelli et al., 2018).

Some of the earliest clinical research to employ agonist-based treatment for StUDs were clinical trials of dextroamphetamine (i.e., dexamphetamine and *d*-amphetamine) for individuals with comorbid cocaine and heroin dependence conducted by Grabowski and colleagues (Grabowski et al., 2001; Grabowski et al., 2004). These double-blinded, placebo-controlled randomized controlled trials (RCTs)—a study design involving the random assignment of individuals to either an experimental or placebo-control condition to evaluate the effectiveness of an intervention—lasted for 12 and 24 weeks, and administered dextroamphetamine (ranging from 15 to 60 mg/day) alongside once-weekly voluntary behavioral sessions. Although these trials exhibited promising potential for reducing cocaine use and craving in this population, the observed improvements in cocaine abstinence-related outcomes relative to control often did not attain statistical significance, likely due to issues of low treatment adherence, low statistical power resulting from small samples, and/or large attrition rates (Grabowski et al., 2001; Grabowski et al., 2004). Similarly, an early pilot RCT by Shearer et al. in the early 2000s (Shearer et al., 2003) identified a similar pattern of non-significant improvement in cocaine abstinence-related outcomes in individuals with cocaine dependence. More recently, during the COVID-19 pandemic, stimulant agonist therapy was employed in British Columbia (Canada) to reduce the risk of COVID-19 exposure during face-to-face treatment for StUDs (Ahamad et al., 2020). A case study details this treatment of an individual with severe StUD (primarily involving methamphetamine use) using immediate-release dextroamphetamine (15–20 mg twice/day; dispensed daily), which markedly reduced their stimulant use and improved their quality of life (Mak et al., 2022).

More recent clinical trials have evaluated the efficacy of sustained-release and/or mixed formulations of amphetamine-based stimulants. In 2016, Nuijten et al (Nuijten et al., 2016). reported that among individuals with treatment-refractory CUD and comorbid OUD, sustained-release dexamphetamine (60 mg/day; 12 weeks) alongside co-prescribed methadone (maximum dose 150 mg, once daily) and diacetylmorphine (i.e., maximum dose 1000 mg, 3 times daily, 7 days/week) treatment reduced days of cocaine use (~16 fewer days, on average) and increased the proportion of individuals able to abstain from cocaine for over 21 days, relative to placebo. Follow-up analyses revealed that sustained-release dexamphetamine in this sample was also associated with greater improvements in overall health, particularly for individuals with poorer overall health at baseline (Blanken et al., 2020). Another Canadian case study of an individual with comorbid StUD and OUD reported that sustained-release dexamphetamine (Dexedrine; 60 mg/day) was well-tolerated with no adverse effects reported, reduced cocaine cravings, and reduced cocaine intake (from an average of 10–15 to 1–2 rocks of crack cocaine on 2 days/week) – benefits that persisted for over 6 months from dose stabilization (Palis et al., 2021). Finally, in their 13-week RCT, Levin et al (Levin et al., 2015). reported that among individuals with comorbid CUD and attention deficit hyperactivity disorder (ADHD), extended-release mixed amphetamine salts (60 or 80 mg/day) alongside once-weekly CBT increased the odds of achieving a cocaine-free week and sustaining abstinence during the final 3 weeks of the trial compared to the control group. Notably, efficacy was higher among those with high impulsivity, indicating that impulsiveness may serve as a moderator of treatment effects (Blevins et al., 2020).

Other clinical trials have tested lisdexamfetamine (LDX), the first approved stimulant pro-drug (Van Meer, 2014), which is taken orally as a pharmacologically inactive compound and converted to its active component (i.e., dexamphetamine) in the blood after absorption. Given concerns about the abuse liability of psychostimulant medications in StUD populations, a potential advantage of LDX is its putative lower abuse potential and improved safety profile compared to immediate-release dextroamphetamine formulations (Van Meer, 2014; Najib, 2009; Jasinski and Krishnan, 2009). Mooney et al (Mooney et al., 2015). conducted the earliest and only RCT assessing the efficacy of LDX (70 mg/day, equivalent to 30 mg dextroamphetamine; 14 weeks) for treating StUDs in a sample of cocaine-dependent treatment-seeking individuals. Although no effect of LDX treatment on cocaine abstinence was identified, individuals receiving LDX treatment reported less severe cocaine craving, and LDX was well-tolerated and generally safe. The remaining evidence for using LDX to treat StUDs is preliminary, consisting of a case study and open-label clinical trials that lack appropriate control groups to ascertain efficacy (i.e., no placebo control). The case study details the treatment of an individual with comorbid MUD and ADHD prescribed LDX (40 mg/day) (Levine and Swanson, 2023); the individual reported using methamphetamine as a form of “self-medication” for their ADHD symptoms. The individual reported that LDX treatment improved their ADHD symptoms, did not exacerbate anxiety or sleep problems, and improved stimulant use-related outcomes, including reducing their cravings and use of stimulants (confirmed via urinalysis) (Levine and Swanson, 2023). As for open-label trials, these have collectively determined that doses of LDX ranging up to 140 mg/day for individuals with CUD (Mariani et al., 2021) and 250 mg/day for individuals with MUD (Ezard et al., 2021) are generally safe and well-tolerated. Furthermore, given that a major barrier to abstinence in stimulant users relates to the aversive withdrawal syndrome experienced during acute abstinence (Li and Shoptaw, 2023), a recent open-label single-arm clinical trial has assessed the safety and feasibility of using LDX as a treatment for methamphetamine withdrawal (Acheson et al., 2022). Acheson et al (Acheson et al., 2022). found that tapering the dose of LDX across 5 days (250 mg/day with 50 mg/day reductions), constituted a safe, tolerable, and feasible for the management of acute methamphetamine withdrawal and craving in treatment-seeking individuals with MUD. Importantly, however, treatment efficacy relative to a placebo control was not assessed in this study. Taken together, these trials contribute preliminary yet foundational evidence for the feasibility of LDX dosing in the context of StUD treatment.

Of the various pharmacological treatments that have been trialed for StUDs, meta-analyses of studies conducted prior to 2020 demonstrated that psychostimulant agonist treatments for StUDs (e.g., dextroamphetamine and LDX) were the only pharmacological treatment class to improve cocaine abstinence-related outcomes (Farrell et al., 2019; Castells et al., 2016; Tardelli et al., 2020). More specifically, psychostimulant treatments increased both rates of sustained stimulant abstinence and duration of abstinence in individuals with StUDs, particularly CUD (Tardelli et al., 2020), although the effect sizes were often small and the quality of evidence was very low due to the high risk of bias (Farrell et al., 2019; Castells et al., 2016). For individuals with CUD, stronger evidence (i.e., of moderate quality) was found for using prescription amphetamines to promote sustained abstinence, with higher doses being associated with greater efficacy in promoting abstinence (Tardelli et al., 2020). While

evidence was assessed as insufficient to support the use of psychostimulant-based treatments for StUDs, it was concluded that further high-quality trials of longer duration evaluating the efficacy of this potential treatment avenue were warranted (Ronsley et al., 2020).

At present, several clinical trials are being conducted to further evaluate the efficacy of these psychostimulant-based treatments for StUDs. In the Netherlands, a double-blinded, placebo-controlled RCT (NCT05529927) is assessing the efficacy of 24-week treatment using sustained-release dexamphetamine (30–90 mg/day) for patients with moderate to severe CUD and comorbid OUD who are also undergoing standard methadone maintenance treatment. In a separate trial, LDX is being tested for the treatment of methamphetamine dependence (the LiMA study; ACTRN12617000657325, Australian New Zealand Clinical Trials Registry) (Ezard et al., 2021) – results are anticipated to be published soon, accounting for delays caused by the COVID-19 pandemic (*Drug Alcohol Rev.*, 2021). This Australian-based Phase 3 trial was a double-blind, placebo-controlled RCT that employed a 15-week treatment of LDX (12-week maintenance at 250 mg/day) for methamphetamine dependence, conducted in conjunction with CBT, to assess treatment efficacy in reducing methamphetamine use. Similarly, a Phase 2 RCT is underway in Canada (NCT05854667), assessing the efficacy of LDX treatment and CM interventions for the treatment of MUD; the LDX component is double-blinded (up to 250 mg/day vs placebo, 15-week), whereas the CM component is open-label. Critically, this clinical trial will compare the efficacy of LDX treatment alone against CM alone, a combination of LDX *and* CM treatment, and placebo with usual care.

The clinical evidence base for psychostimulant-based agonist treatments for StUDs is clearly still emerging, and much further research will be required to establish optimal treatment avenues; however, the extant preliminary evidence demonstrates promising therapeutic potential for the much-needed treatment of these SUDs. As a research agenda, future research in this space should continue to identify optimal agonist doses and ascertain predictors of best doses that could be used for screening purposes, and continue to optimize and develop different formulations potentially including combination treatments that allow lower doses to minimize side effects while achieving synergistic effects and modulate diverse neurotransmitter/receptor systems affected by stimulant use (Stoops and Rush, 2014). Moreover, a combination of short-acting and long-acting stimulants may help to combat the continued use of cocaine despite treatment since individuals may continue to use illicit stimulants with quicker onset effects not provided by sustained-release dextroamphetamine or LDX (Dürsteler and Vogel, 2016). It has been suggested that it is possible that distinct treatments will be required for individuals with CUD and MUD based on the distinct aspects of their neurobiological mechanisms of action (Stoops and Rush, 2013); thus, future trials should compare the efficacy of unique psychostimulant treatments for CUD vs MUD populations. Many of the clinical trials reviewed here involved daily supervised administration of medication in an outpatient setting, which is resource-intensive and interferes with patient autonomy (Nuijten et al., 2016). Thus, future research should also aim to assess treatment compliance and address this explicitly via co-implementation of compliance-enhancing interventions alongside psychostimulant-based treatment. The potential for abuse for all prospective psychostimulant-based treatments among StUD patients, as well impacts of these medications on appetite and sleep in StUD

patients (Armanious et al., 2024), must also be exhaustively characterized. Lastly, given the evidence that combining CM with pharmacological interventions produced superior treatment effects, future clinical trials should evaluate the efficacy of these psychosocial interventions in the context of psychostimulant-based pharmacotherapies for StUDs (Tardelli et al., 2018).

3. Psychedelics and the 5-HT2 A receptor

Classic psychedelics are a unique drug class that produce altered states of consciousness, perception, mood, and cognition via serotonin 2 A (5-HT2A) agonism. The most commonly researched classic psychedelics include psilocybin, lysergic acid diethylamide (LSD), *N,N*-dimethyltryptamine (DMT), 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), mescaline, and the dissociative psychedelic ibogaine. Over the last decade, there has been a rapid surge in psychedelic clinical trials for SUDs, becoming the second-most studied class of psychiatric disorder behind major depression.

Psychedelics are most often leveraged in the psychedelic-assisted treatment model, which argues that these acute psychedelic experiences within a controlled therapeutic context can elicit deep insight, and emotional, cognitive, and behavioral changes that result in positive long-term mental health outcomes (Ziff et al., 2022). Psychedelic-assisted psychotherapy has shown preliminary efficacy toward treating SUDs. A meta-analysis of six RCTs for LSD in human alcohol addiction reported that a single dose of LSD reduces alcohol misuse (Krebs and Johansen, 2012). More recently, a proof-of-concept clinical study of psilocybin-assisted psychotherapy for AUD found that participants receiving two doses of psilocybin as an adjunct to psychosocial intervention decreased alcohol consumption by 26% compared to baseline (Bogenschutz et al., 2015). Replication using a double-blinded placebo-controlled design found a mean difference of 13.9% between treatment groups in heavy drinking days after a 32-week follow-up period (Bogenschutz et al., 2022). Furthermore, an open-label pilot study using psilocybin-assisted psychotherapy to treat nicotine addiction found that 80% of participants were abstinent at the 6-month follow-up (Johnson et al., 2014) and 67% at 12 months (Johnson et al., 2017). Despite these promising findings, the clinically relevant mechanisms of action for psilocybin are not well understood, and concerns around expectancy biases and placebo effects somewhat shroud positive outcomes. Concurrently though, preclinical neurobiological studies are revealing potential causal mechanisms of action, which increase confidence in these clinical effects.

There are multiple emerging hypotheses of how psychedelics may ameliorate symptoms of SUDs. Psychedelics induce neuroplasticity through activation of the 5-HT2A receptor, primarily in the prefrontal cortex. The prefrontal cortex is vital for executive function and control of high-level cognitive and emotional processes (Diamond, 2013). Accordingly, 5-HT2A receptors are densely expressed in layer V glutamatergic pyramidal neurons in the prefrontal cortex. In vivo and in vitro studies in rodents indicate that a single dose of psilocybin is associated with long-lasting increases in dendritic and synaptic growth in the prefrontal cortex (Ly et al., 2018; Shao et al., 2021). The transition toward uncontrolled drug-seeking/use in SUDs is associated with drug-induced neuroplasticity in the cortico-striatal pathway (Lüscher et al., 2020); psychedelics may open a window of neuroplasticity

in this pathway that can be leveraged in psychotherapy to induce long-lasting effects beyond acute drug administration. Alternatively, the therapeutic effects of psychedelics may be linked with their anti-inflammatory properties. Chronic drug consumption results in elevated TNF-a, IL-1B, and IL-6 levels in the rodent brain, which have been linked to neurodegeneration and reduced cognitive capabilities (Zhao et al., 2013; Wang et al., 2018); these effects might be counteracted by psychedelics that have anti-inflammatory properties (Flanagan and Nichols, 2018). Consistent with this, it was recently reported that psilocybin (3 mg/kg; i. p.) treatment prior to a cued reinstatement test of heroin seeking was associated with reduced levels of the cytokine IL-17a and its corresponding receptor, *Il17ra*, in the prefrontal cortex (Floris et al., 2024). Further, selective inhibition of IL-17a signaling in the PFC was sufficient to reduce heroin-seeking behavior (Floris et al., 2024), potentially linking IL-17a signaling to psilocybin's therapeutic action. Consequently, biomarkers of neuroinflammation are increasingly being collected in SUD clinical trials.

SUDs are often associated with impaired cognitive function, and cognitive deficits are predictive of drug use frequency and relapse outcomes (Ceceli et al., 2022). For instance, cognitive inflexibility is a significant predictor of addiction-related outcomes in animal models (e.g., Istin et al., 2017, whereby poor performance on a set-shifting task predicted methamphetamine self-administration) and in clinical studies (e.g., Karabulut, 2023 whereby perseverative errors in the Wisconsin Card Sorting Task predicted increased methamphetamine use). To this end, it is interesting that a recent study reported that psilocybin improves cognitive flexibility in a preclinical deficit model of anorexia nervosa (Conn et al., 2024), a phenotype regulated by aberrant corticostriatal activity (Milton et al., 2021), and that a clinical trial of psilocybin for the treatment of major depression reported improved cognitive flexibility for up to 4-weeks following treatment (Doss et al., 2021). Thus, psychedelics might produce enduring improvements to cognitive flexibility, enabling patients to better engage with psychotherapy, regain top-down control over reward-related decision-making, and more readily form new behavioral patterns that promote abstinence and reduce relapse.

Collectively, there is a compelling neurobiological rationale for how psychedelics, likely via 5-HT2A activity, might produce long-term changes to brain function and behavior relevant to the treatment of SUDs. Importantly, over the coming years, dozens of SUD clinical trials will be reported on, which will determine whether this class of compounds receives regulatory approval for use for treatment of SUDs. While the field awaits these outcomes, there is substantial research efforts currently underway to explore the hypotheses detailed above and, additionally, to develop novel psychedelic-inspired compounds with improved drug-like properties and accessibility. The latter is driven largely by concerns around access: psychedelic-assisted therapy will be financially costly and likely inaccessible to many patients who are not located in close proximity to approved treatment centers. Additionally, due to the hallucinogenic effects of therapeutic doses of psychedelics, many patients are currently excluded from clinical trials, including those with a family or personal history of psychosis. These exclusions are potentially necessary for safety, although this does preclude a large proportion of patients with drug-related psychosis, who often have the highest disease burden, from accessing these potentially beneficial treatments.

A potential solution to these access issues is the development of 5-HT2A agonists, which do not require intense medical supervision as they do not produce hallucinations, and yet retain their enduring therapeutic effects. However, it is currently unknown whether the hallucinogenic state, psychotherapy, or their interaction, is required for the enduring therapeutic effects of psychedelics. Partly addressing this uncertainty, recent data reported by the biopharmaceutical company MindMed (developing LSD as MM120) that a single hallucinogenic dose of LSD, in the absence of psychotherapy, can produce dose-dependent and enduring reductions to anxiety symptoms (Mind Medicine, 2024). This supports the notion that—at least for generalized anxiety disorder—the psychotherapy component may not be required for therapeutic efficacy. There is also preclinical data indicating that psychedelic analogues, which lack hallucinogenic-like effects in animals, retain their effects in reducing heroin and alcohol consumption (Bonilla et al., 2024). This finding is particularly promising as biotechnology company Delix Therapeutics has reported on Phase I clinical safety and tolerability of their lead psychedelic-analogue compound, DLX-001, which lacks hallucinogenic effects in people and yet has neuroplasticpromoting effects in animal models. Although DLX-001 is being developed for mood disorders, Delix have received funding to develop other compounds from their library for the treatment of SUD (Delix Therapeutics, 2024). Similarly, biotechnology company Psylo have received funding to develop non-hallucinogenic 5-HT2A agonists for the treatment of MUD (Psylo, 2024). While these approaches remain unproven, it is possible that within the next few years, there will be several hallucinogenic (e.g., psilocybin, LSD) and novel non-hallucinogenic 5-HT2A agonists in clinical development for SUDs with commercial backing.

4. Glucagon-like peptide 1 (GLP-1) receptor agonists

Among the emerging medications currently being trialed for SUDs, GLP-1 receptor agonists have perhaps attracted the most attention, in part because of their popularity as weight loss medications. Endogenous GLP-1 is produced by cleavage of the prohormone, preproglucagon, in the intestines and is released in response to food intake (Holst, 2007). GLP acts at GLP-1 receptors (GLP-1Rs) to stabilize blood glucose levels by stimulating insulin secretion (‘incretin effect’) and inhibiting glucagon production (Holst, 2007). GLP-1 is degraded by the ubiquitous enzyme dipeptidyl peptidase-4 (DPP-4); thus, there has been significant effort dedicated to developing long-acting stable receptor agonists of GLP-1R (GLP-1RAs; so-called ‘incretin mimetics’) for the management of type 2 diabetes (T2D) and associated conditions, including overweight and obesity (Müller et al., 2019).

The first in this new class of incretin mimetics was exenatide (Byetta; Eli Lilly), a GLP-1RA with a half-life of ~2 hours following s.c. injection, which was approved in the US in 2005 for the treatment of T2D. Subsequently, liraglutide (Victoza, Novo Nordisk) was developed to have a longer half-life (~13 hours) and was approved in the US for the treatment of T2D and weight loss in 2010 and 2014, respectively. The more recently developed GLP-1RA, and the one that has gained the most notoriety, is semaglutide, which has been formulated for both s.c. (half-life: ~1 week) and oral (half-life: ~1 day) administration and approved for both T2D (Ozempic, Novo Nordisk, approved in 2017) and weight loss (Rybelsus) indications. Although favorable clinical weight/T2D outcomes have been reported for all GLP-1RAs, these effects are profound with semaglutides, including substantial decreases in

body weight (8–16%) and improvements in glycemic control (i.e., HbA_{1c} levels) (Rubino et al., 2021; Wadden et al., 2021; Wilding et al., 2021). Most importantly, with respect to their potential repurposing for SUDs, GLP-1RAs are generally safe and well-tolerated, with the most common side effects being mild gastrointestinal complaints. Their regulatory approval and widespread use make the potential repurposing of these compounds for SUDs theoretically straightforward. The case for repurposing these medications for SUDs, as well as the important considerations for this approach, has been discussed at length in several recent excellent publications (Klausen et al., 2022a; Leggio et al., 2023) and thus here we provide only a brief overview of this topic.

Following their widespread clinical adoption for managing T2D and associated conditions, anecdotal patient reports began to emerge, indicating that GLP-1RAs also reduced the desire to use alcohol and nicotine (Leggio et al., 2023). Combined with an increased appreciation that similar neural circuits govern the overconsumption of food and drug intake (Brown et al., 2022; Brown and James, 2023), there has been widespread interest in investigating the potential utility of these compounds for the management of various SUD-related outcomes. Studies in laboratory animals, including non-human primates, have consistently demonstrated that GLP-1RAs reduce intake and motivated responding for alcohol, cocaine, nicotine and opioids (Urbanik et al., 2022; Marty et al., 2020; Douton et al., 2022; Hernandez et al., 2021; Fink-Jensen et al., 2024). These effects appear to be mediated via actions at a distributed network of reward regions in the brain, including ventral tegmental area (Shirazi et al., 2013), lateral hypothalamus (Colvin et al., 2020) and nucleus accumbens (Colvin et al., 2020), as infusions of GLP-1RAs directly into these regions partly recapitulates the effects of systemic administration. Significant advances have been made in recent years with respect to characterizing the specific cell types in the brain that express GLP-1Rs, and their role in mediating the effects of GLP-1RAs on addiction-relevant behaviors – these are elegantly discussed elsewhere (Klausen et al., 2022a).

Despite widespread enthusiasm, currently, there is scant data supporting the efficacy of GLP-1RAs in clinical SUD populations (Leggio et al., 2023). This largely reflects the fact that dedicated RCTs designed to test these compounds have only recently been established and are ongoing. Perhaps the best evidence to date supporting their efficacy comes from a nationwide registry study in Denmark of all new users of GLP-1RAs (n = 38,454) and dipeptidyl peptidase 4 inhibitors (n = 49,222) between 2009 and 2017. Individuals were tracked for hospital contacts or medication purchase associated with treatment for AUD over a period of 4 years. Analyses revealed that GLP-1RA treatment was associated with a lower incidence of an alcohol-related event, but only during the initial 3 months after the start of treatment (Wium-Andersen et al., 2022). To date, only one RCT has tested a GLP-1RA – exenatide – in an SUD population. This study, conducted in treatment-seeking AUD patients, reported that exenatide had no effect compared to placebo on the number of heavy drinking days (Klausen et al., 2022b). However, other analyses indicated that exenatide significantly attenuated fMRI alcohol cue reactivity in several reward regions, including the ventral striatum and septum, and significantly reduced alcohol intake among participants with comorbid AUD and obesity (Klausen et al., 2022b). These mixed findings underscore the need for more RCTs in SUD patients; these studies will be critical for determining whether GLP1-RAs live up to the considerable excitement surrounding their

potential repurposing (Leggio et al., 2023). To this end, it is notable that several clinical trials are currently ongoing across several SUD classes, including RCTs testing exenatide in CUD (NCT04941521; NCT06252623) patients, and semaglutide in AUD (NCT06015893; NCT05891587), OUD (NCT06548490) and NUD (NCT05530577) patients.

5. Cannabidiol and related cannabinoid receptor modulators

Medicinal use of the *Cannabis sativa* plant dates back millennia (Crocq, 2020). The plant contains approximately 120 identified cannabinoids, which are proposed to be the primary class of psychotropic compounds found in the plant (ElSohly and Gul, 2014). The most abundant and researched cannabinoids isolated from the plant are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD); THC is responsible for the intoxicating effects of cannabis, while CBD is the major non-intoxicating component of the plant (Chye et al., 2021). In part due to its lack of intoxicating effects, CBD has been extensively studied in both animal models and—increasingly—in clinical studies. CBD, in the form of Epidiolex®, is FDA-approved for the treatment of seizures in Dravet and Lennox-Gastaut syndromes (Greenwich, 2020). However, due to CBD's capacity to reduce anxiety- and depression-like symptoms (García-GutIérrez et al., 2020), alongside its neuroprotective (Bhunia et al., 2022), anti-seizure (Nabbout and Thiele, 2020), and anti-inflammatory properties (Atalay et al., 2019), evidence supports the potential therapeutic efficacy of CBD for a range of other disorders, including SUDs.

Substantial preclinical evidence supports the potential utility for CBD to reduce drug-related behaviors. CBD dose-dependently reduced ethanol self-administration and consumption in rodents in operant, two-bottle choice, and drinking-in-the-dark paradigms (Maccioni et al., 2021; Viudez-Martínez et al., 2020; Viudez-Martínez et al., 2018). Notable is that higher doses of CBD are required in female rodents to obtain an equivalent reduction in drinking as males (Viudez-Martínez et al., 2020). In rodents, CBD also attenuates the expression of alcohol CPP (Andaloussi et al., 2021), primed reinstatement of ethanol seeking (Viudez-Martínez et al., 2018), and context- and stress-induced reinstatement (Gonzalez-Cuevas et al., 2018). Despite these findings in rodents, the only published study of CBD administration in nonhuman, alcohol-dependent primates (i.e., baboons) failed to influence alcohol intake (Moore et al., 2023). This inconsistency may be due to the species difference, the baboons' history of chronic drinking (mean > 10 years), and the oral route of administration considering the low oral bioavailability of CBD (compared to i.p. or transdermal administration in rodent studies) (Franco and Perucca, 2019). Beyond the suppressant effects of CBD on alcohol intake and reinstatement, CBD exerts a range of other beneficial influences in preclinical models, including normalizing somatic withdrawal signs and anxiety-like behaviors in mice undergoing alcohol withdrawal (Gasparyan et al., 2023), reducing ethanol-related liver damage in mice (Wang et al., 2017; Yang et al., 2014), and ethanol-related hippocampal and cortical neurodegeneration in rats (Hamelink et al., 2005; Liput et al., 2013). The beneficial effects of CBD for other SUD preclinical models (e.g., opioid and psychostimulant use) are consistent with those observed in AUD models. For example, in rodent models of OUD, CBD attenuated reinstatement to heroin-seeking (Ren et al., 2009), blocked the reward-facilitating effects of morphine (Katsidoni et al., 2013), attenuated morphine-induced CPP (de Carvalho and Takahashi, 2017; Markos et al., 2018),

and alleviated heroin- and oxycodone-induced withdrawal signs (Navarrete et al., 2022; Scicluna et al., 2024). Similarly, in StUD models, CBD reduced cocaine self-administration and cocaine-induced CPP (Gonzalez-Cuevas et al., 2018; Galaj et al., 2020; Luján et al., 2018), reduced methamphetamine self-administration in rodents (Hay et al., 2018), attenuated methamphetamine reward seeking in the CPP paradigm (Karimi-Haghighi and Haghparast, 2018; Mohammadi et al., 2023; Yang et al., 2020), and alleviated behavioral signs of cocaine withdrawal (Gasparyan et al., 2021). The consistency of CBD's effects across alcohol and other substances may suggest that common therapeutic mechanisms are involved.

Despite a compelling preclinical evidence base, the clinical evidence supporting the use of CBD for AUD and other SUDs is relatively preliminary. An observational study of individuals who use both alcohol and cannabis found that unrestricted use of CBD-dominant cannabis (1% THC, 24% CBD)— compared to THC-dominant and THC/CBD balanced cannabis—for 5 days reduced reported days of drinking and drinks per drinking day (Karoly et al., 2021). However, at present, no clinical trials of CBD for AUD have been published. Nevertheless, several clinical trials have recently been completed (NCT03252756, NCT03248167), which will provide much-needed insight into understanding the efficacy and safety of CBD to treat AUD. The ClinicalTrials.gov registry also details several other RCTs – currently underway or recruiting – examining the behavioral and neurobehavioral effects of CBD in AUD populations (NCT05613608, NCT05159830, NCT06512389, NCT05860699, NCT05387148, NCT05317546, NCT04873453, NCT05389930). For example, a study protocol by Hurzeler et al (Hurzeler et al., 2024). (NCT05387148) describes a double-blind RCT that will investigate the efficacy of CBD (800 mg/day; p.o.) in treating AUD using neuroimaging techniques and a wide range of cognitive, behavioral, and physiological assessments. Taken together, the extant clinical evidence is insufficient to ascertain whether CBD represents an efficacious treatment for AUD however, the high number of clinical trials addressing this question indicates a high degree of interest in evaluating its therapeutic potential.

In the context of other SUDs, preliminary clinical evidence of efficacy is available for OUD and cannabis use disorder. Hurd et al (Hurd et al., 2019). conducted a double-blinded RCT, which found that CBD (400 or 800 mg/day for 3 days) reduced cue-induced craving and anxiety in individuals with OUD (i.e., heroin use disorder), compared to placebo. Furthermore, several clinical trials examining CBD's efficacy to treat opioid use disorder are currently underway (NCT06206291, NCT05299944, NCT04587791, NCT04587791). The first RCT evaluating the efficacy of CBD for individuals with cannabis use disorder demonstrated that CBD (400 or 800 mg; p.o.) reduced cannabis use compared to placebo (Freeman et al., 2020). This effect is being explored further in a large (n = 250) Phase III multisite RCT exploring CBD's effects on cannabis use, cravings, and cognitive function (Bhardwaj et al., 2024). Several other clinical trials of CBD for other SUDs are also completed and/or ongoing, including cocaine use (NCT02559167 and NCT06159387), tobacco use (NCT06218056 and NCT05445804).

Notably, there is a strong association between SUDs, mood, and anxiety disorders, and such comorbidities are known to influence the severity and course of SUDs (Lai et al.,

2015). Given the large body of preclinical evidence supporting the anxiolytic-, antistress-, and antidepressant-like effects of CBD (García-Gutiérrez et al., 2020), these properties of CBD likely contribute to its effects on substance use behaviors (Navarrete et al., 2021). However, CBD's broad pharmacological profile (Martin et al., 2021; Morales et al., 2017) and its ability to diminish drug-related reward suggest that targets beyond solely anxiolytic and anti-stress mechanisms are also likely involved in its therapeutic capacity.

Pharmacologically, CBD interacts with and modulates the activity of several G-protein-coupled receptors—only some of which belong to the endogenous cannabinoid system. The endocannabinoid system comprises cannabinoid type-1 and type-2 receptors (CB_1R and CB_2R), together with their endogenous ligands (endocannabinoids), and the enzymes responsible for their synthesis, reuptake, and degradation (Marzo et al., 2004). Although CBD can antagonize the CB_1R and CB_2R, it has low affinity for the orthosteric binding site of these receptors (McPartland et al., 2015). The in vitro characterization of CBD as a negative allosteric modulator of CB_1R by Tham et al (Tham et al., 2019),. together with in vivo results showing the moderation of excessive alcohol drinking by CB_1R antagonists AM251 (Femenía et al., 2010) and SR141716A (Getachew et al., 2011), indicate that antagonism or negative allosteric modulation of cannabinoid receptors represent a potential mechanism involved in CBD effects on drug intake (at least in the case of alcohol). In fact, to this point, a novel pharmacological agent has been developed for the treatment of cannabis use disorder (CaUD; Phase 2 testing completed), which currently has no approved pharmacological treatments; AEF0117 (Indivior)—a 'signaling-specific CB_1R inhibitor'—binds to an allosteric site on CB_1R and inhibits specific intracellular signaling pathways without altering ligand binding, which facilitates the functional inhibition of several THC-induced consequences at CB_1R in the absence of other behavioral consequences of CB_1R antagonism (Haney et al., 2023). Recent evidence from clinical trials (NCT03325595, NCT03443895, and NCT03717272) has indicated that AEF0117 represents a safe and well-tolerated treatment avenue in healthy individuals and those with CaUD, and that AEF0117 reduced the positive subjective consequences of cannabis (0.06 and 1 mg) and cannabis self-administration (1 mg) in individuals with moderate to severe CaUD (Haney et al., 2023). Thus, allosteric modulation of the CB_1R, whether via CBD, AEF0117, or related pharmacological agents currently in the pipeline, may prove promising treatment options for CaUD and other SUDs in the future.

Beyond the cannabinoid system, CBD interacts with various other non-cannabinoid receptors that likely also mediate its therapeutic effects; one of the most characterized targets is the serotonin-1 A receptor ($5\text{-}HT_{1A}R$). Rock et al (Rock et al., 2012). characterized CBD as a positive allosteric modulator of the $5\text{-}HT_{1A}R$, which enhanced binding at the $5\text{-}HT_{1A}R$ at a relatively low CBD concentration (i.e., 0.1 μM). In fact, $5\text{-}HT_{1A}R$ activation is the mechanism most frequently linked to the effects of CBD in vivo, particularly in the context of its anxiolytic-like and antidepressant-like effects (García-Gutiérrez et al., 2020). This interaction is therapeutically significant given evidence indicating a role of $5\text{-}HT_{1A}Rs$ in mood disorders (Albert and Vahid-Ansari, 2019) and SUDs (Navarrete et al., 2021). CBD also interacts with the serotonin-3 receptor ($5\text{-}HT_3R$), acting as an antagonist (Yang et al., 2020). In animals, $5\text{-}HT_3R$ antagonists attenuate cocaine and morphine-induced increases in extracellular dopamine levels in striatum (McNeish et al., 1993; Kankaanpää et al., 2002;

Pei et al., 1993), and (under some circumstances) reduce self-administration of these drugs (Davidson et al., 2007; Hui et al., 1993). In clinical AUD populations, 5-HT_3R antagonist medications have successfully reduced alcohol consumption and craving (Fakhfouri et al., 2019), consistent with microdialysis studies showing that 5-HT_3R blockade prevented the alcohol-induced release of dopamine in reward circuitry (Campbell et al., 1996; Campbell and McBride, 1995).

CBD is also an agonist at the peroxisome proliferator-activated receptor-gamma (PPARɣ) (O'Sullivan et al., 2009), an interaction that is implicated in CBD's anti-inflammatory and neuroprotective effects (Esposito et al., 2011). Other PPARɣ agonists, including the drugs pioglitazone and rosiglitazone, and the *Andrographis paniculata* plant, lower alcohol and opioid intake in rodent models (Domi et al., 2020; Stopponi et al., 2021; Stopponi et al., 2011; de Guglielmo et al., 2015), and block the expression of behavioral sensitization to methamphetamine (Maeda et al., 2007), possibly via attenuation of mesocorticolimbic dopamine activity (Fotio et al., 2021). Additionally, given the inflammatory consequences of chronic substance use and associated neural dysfunction (Ahearn et al., 2021; Smiley and Wood, 2022), PPARɣ activation by CBD may protect and/or promote neuroimmune functioning in SUDs by inhibiting proinflammatory transcriptional factors and promoting neurogenesis (Cippitelli et al., 2017; Robinson et al., 2014). However, evidence for the clinical efficacy of PPARɣ agonism using pioglitazone in the treatment of SUDs is still preliminary (Jones, 2020); pioglitazone reduced craving for heroin (Jones et al., 2018), nicotine (Jones et al., 2017), and cocaine (Schmitz et al., 2017) in RCTs of substance-dependent individuals but did not impact the abuse potential of these substances (i.e., drug use and positive subjective effects). Thus, multiple targets and mechanisms exist through which CBD *may* act to modulate consumption and the effects of misused substances. However, the involvement of these mechanisms in CBD effects on addictive behaviors is, at present, largely hypothetical, and further research is needed to ascertain the causal significance of these targets in CBD's effects in SUD models. Notably, these known targets of CBD, and potentially others yet to be identified, may contribute independently or synergistically to effects relevant to the treatment of SUDs.

Overall, CBD displays a favorable safety profile (Tang et al., 2022) and—provided this is maintained in clinical trials—ongoing examination will contribute to the understanding of CBD's potential efficacy to treat SUDs. However, some pharmacodynamic and pharmacokinetic limitations of CBD could hinder its progression into the clinic. Natural compounds like cannabinoids are pharmacologically "promiscuous", and whilst this can be seen as an advantage if activity is distributed across multiple disease-relevant targets, interactions with off-target mechanisms could increase the likelihood of adverse effects (Kabir and Muth, 2022), an issue compounded by the relatively high doses of CBD that appear to be required to elicit effects. It is also important to note that whilst CBD does interact with several targets of potential relevance to the treatment of substance use disorders, these interactions are relatively low-to-low potency among the interactions described here (e.g., IC50 of 0.6 μM at 5-HT_3R) (Yang et al., 2010). Moreover, CBD is known to inhibit the enzymatic metabolism of several other commonly prescribed drugs, increasing the risk of drug-drug interactions (Bansal et al., 2022). More generally, the pharmacokinetic profile of CBD is less than desirable, including low oral bioavailability,

variability in absorption depending on the fed state (i.e., whether consumed with food or without), and a variable half-life ranging from 1 hour to 5 days depending on the route of administration and dose (Millar et al., 2018). Nonetheless, even if CBD itself is a less-than-optimal therapeutic, determining how CBD exerts effects relevant to SUDs may identify novel targets that can become the focus of target-based drug discovery. Thus, although CBD is not without its limitations, ongoing investigation as an emerging medication in the context of SUDs is likely to produce some benefit.

6. Kappa opioid receptor antagonists for SUD-induced negative affective withdrawal states

The kappa opioid receptor (KOR) is one of five opioid receptors expressed in the brain and is targeted primarily by the dynorphin family of endogenous opioids, including dynorphin-A, which is cleaved from prodynorphin (Shippenberg, 2009). Dynorphin (Dyn) peptides and KORs are expressed throughout cortical, striatal, and limbic regions, with a high concentration in the mesolimbic dopaminergic pathway from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) (Hurd, 1996; Knoll and Carlezon Jr., 2010; Tejeda and Bonci, 2019a). Dyn/KOR signaling in the NAc has been implicated in both reward and aversive processes (Al-Hasani et al., 2015) and emerging evidence suggests that modulation of this system may represent a promising approach for treating SUDs (Reed et al., 2022)—particularly in addressing the negative affective states associated with withdrawal following chronic use of substances like alcohol (Sureshkumar et al., 2022; Chavkin and Koob, 2016) and opioids (Tejeda and Bonci, 2019a; Sureshkumar et al., 2022). These abstinence-induced negative affective states drive ongoing drug-seeking through negative reinforcement mechanisms long after acute withdrawal symptoms have subsided (Koob, 2021; Koob and Volkow, 2016). This negative reinforcement is hypothesized to occur via Dyn/KOR signaling modulating dopaminergic tone, producing a negative affective state characterized by dysphoria and aversion (Tejeda and Bonci, 2019a). Given that no current pharmacotherapies are indicated specifically for the negative affective symptoms associated with SUDs, the Dyn/KOR system represents a promising therapeutic target, especially within the context of OUD and AUD.

Preclinical studies broadly indicate that chronic opioid exposure activates the Dyn/KOR system within the mesolimbic pathway (Solecki et al., 2009), promoting negative affect (Tejeda and Bonci, 2019b). For example, in mouse models, chronic morphine administration followed by a 4-week forced abstinence period induces depressive-like behaviors accompanied by increases in prodynorphin mRNA and protein levels in the NAc (Zan et al., 2015). Systemic administration or intra-accumbal infusions of the KOR antagonist norbinaltorphimine (norBNI) suppresses the expression of opioid withdrawal-induced depressive-like behaviors, and conditional knockdown of KOR within the NAc similarly attenuates the depressive-like state induced by opioid withdrawal in mice (Zhang et al., 2023). Supporting these pharmacological antagonism studies, KOR knockout mice display less severe social deficits during morphine and heroin abstinence (Lutz et al., 2014; Lalanne et al., 2017). Taken together, preclinical evidence indicates that KOR antagonism is

a promising target for the treatment of negative affective states during opioid withdrawal due to aberrant mesolimbic signaling.

The Dyn/KOR system also plays a key role in the negative affective symptoms of alcohol withdrawal and stress-mediated consumption (Anderson and Becker, 2017; Walker et al., 2012). Rodent strains predisposed to consume more ethanol have an upregulated Dyn/KOR system, and KOR antagonism reduces both negative affect during withdrawal and ethanol consumption (Anderson and Becker, 2017). Administration of CERC-501 (now known as 'aticaprant', described below), a clinical-stage KOR antagonist, blocked relapse to alcohol seeking induced by stress, but not cue-induced reinstatement of alcohol-seeking behavior in rats (Domi et al., 2018), indicating specific effects on stress-mediated consumption. Similarly, forced swim stress-induced ethanol intake is reduced by systemic administration with the KOR antagonist norBNI, while administration of KOR agonists increased ethanol preference (Sperling et al., 2010; Jarman et al., 2018). As with opioids, chronic alcohol exposure alters the Dyn/KOR system across several brain regions involved in negative affect and the regulation of stress, including the central amygdala, bed nucleus of the stria terminalis, and NAc (Sureshkumar et al., 2022; Karkhanis and Al-Hasani, 2020; Pirino et al., 2023), and modulation of KOR signaling in these regions alters alcohol consumption and associated negative affective states (Pirino et al., 2023; Anderson et al., 2019; Kissler and Walker, 2016; Haun et al., 2020).

In light of these preclinical data, there has been considerable interest in developing KOR antagonists for the clinical treatment of SUDs, particularly following their inclusion on the National Institute of Drug Abuse's (NIDA) top-10 hit list of potential therapeutic targets (Rasmussen et al., 2019). There are two FDA-approved compounds for SUDs that have antagonist activity at the KOR, including buprenorphine and naltrexone. Buprenorphine is an agonist at mu-opioid receptors while also acting as an antagonist at delta-opioid receptors and KORs (Coe et al., 2019), whereas naltrexone, approved for both OUD and AUD, is an antagonist at KORs and mu-opioid receptors (Varga, 2014). Given their non-specific effects on the KOR, it is challenging to determine whether any of their therapeutic effects are specifically attributable to KOR antagonism. At present, no selective KOR antagonists have received FDA approval, partly due to several challenges associated with their development. For example, norBNI is a highly potent and selective KOR antagonist; however, it has an extremely long duration of action, which limits its clinical viability (Munro et al., 2012). Additionally, some KOR antagonists have demonstrated toxic effects in animals and humans; for example, Pfizer's PF-4455242, which progressed to Phase I trials for mood disorders and SUDs, demonstrated toxicity in animal studies when administered long-term (Urbano et al., 2014) (NCT00939887). Similarly, the development of JDTic, a selective and reversible KOR antagonist, was discontinued during Phase I clinical trials due to non-sustained ventricular tachycardia (Buda et al., 2015), while AZ-MTAB, developed by AstraZeneca, exhibited high human ether-a-go-go-related gene (hERG) activity, preventing its entry into clinical trials due to safety concerns (Urbano et al., 2014). It is unclear whether these adverse effects are related to the 'on-target' effects of each compound at KOR, or if they each coincidentally had off-target liabilities. Furthermore, translation of the effects of KOR antagonism from animal models to humans has been lackluster. For example, while KOR antagonism showed promising results in preclinical rodent models of CUD, these

findings have not translated to non-human primates or humans (Banks, 2020). However, there does not appear to be published human studies evaluating KOR antagonists in other SUDs, including MUD, OUD, or AUD. Therefore, despite these barriers, the promising preclinical data warrant further efforts to develop novel KOR antagonists for substance use disorders.

The most promising KOR antagonists in current development appear to be aticaprant and CVL-354. A short-acting selective KOR antagonist, aticaprant (also known as JNJ-67953964, Opra Kappa, LY2456302, CERC-501) has rapid oral absorption and a shorter half-life compared to earlier compounds. Originally developed by Eli Lilly and currently under development by Janssen for major depressive disorder (MDD), this compound has shown safety and tolerability in single ascending dose (SAD), and multiple ascending dose (MAD) studies (Lowe et al., 2014), and demonstrated robust engagement with (Zheng et al., 2013) and antagonism of the KOR (Krystal et al., 2020). The compound has undergone substantial preclinical and clinical testing (Schmidt et al., 2024) for depression demonstrating promising results (Wong et al., 2024). In one 8-week study, aticaprant treatment was associated with a gradual reduction of anhedonia symptoms alongside altered ventral striatal activity as assessed by fMRI during reward-based tasks (Krystal et al., 2020), supporting the mechanistic rationale for antagonizing striatal Dyn/KOR signaling in the treatment of negative affect associated with SUDs. However, clinical studies in the context of SUDs are somewhat limited and so far, have yielded underwhelming outcomes. In healthy people diagnosed with cocaine dependence in early abstinence (< 2 months) and drug-free former cocaine-dependent persons (7-month to 25-year abstinence), aticaprant had no effect on depression or cocaine craving scales (Reed et al., 2018). In this study, the environment was designed to minimize stress, and therefore, baseline scores on the depression and craving measures were relatively low, which may have obfuscated any therapeutic effects. Similarly, in a double-blind, placebo-controlled crossover study in cigarette smokers, 8 days of aticaprant administration had no effect on smoking behavior, craving, mood, anxiety, or withdrawal symptoms (Jones et al., 2020). Notably, aticaprant has not yet been clinically investigated for its effects in AUD or OUD, where the rationale for Dynorphin/KOR targeting in arguably strongest. CVL-354 is a novel, brain penetrant, and selective KOR antagonist in clinical development, which was originally developed by Cerevel Therapeutics but was recently acquired by AbbVie who are developing the compound for the treatment of major depressive disorders. CVL-354 has undergone Phase 1 Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) studies (NCT05138653), and a PET trial to evaluate its KOR and mu-opioid receptor occupancy in healthy humans (NCT05547542). However, the results have not been published and it is unclear if this compound is being pursued for a SUD indication. Nonetheless, these compounds demonstrate adequate safety and tolerability, which, coupled with the compelling preclinical data and neurobiological rationale, warrant further exploration in SUD patient populations.

7. Orexin (hypocretin) receptor antagonists to reduce drug craving and improve sleep in SUDs

The orexin (also known as ‘hypocretin’) system has experienced a dramatic surge of interest in recent years as a new target for medications to treat all SUDs (James and Aston-Jones, 2020). This enthusiasm reflects a compelling and extensive collection of preclinical evidence that universally points to the orexin system as a regulator of drug craving and motivation more broadly (Mohammadkhani et al., 2024). First discovered in 1998 by two independent groups, the orexin peptides A and B are produced by a discrete population of neurons in caudal lateral hypothalamus and exert their actions via two G-protein coupled receptors, orexin 1 (Ox1R) and orexin 2 (Ox2R) receptor (de Lecea et al., 1998; Sakurai et al., 1998; Marcus et al., 2001). Extensive preclinical studies have since implicated the orexins in many physiological processes relevant to addiction, including reward motivation, craving, stress and arousal/wakefulness (Mahler et al., 2014), making this system an attractive target for novel medications designed to treat the multifaceted nature of SUDs (James et al., 2017; Mehr et al., 2021).

A general role for the orexins in drug reward was first reported in 2005, when it was demonstrated that orexin neurons are activated in rats expressing a conditioned place preference for cocaine and morphine (Harris et al., 2005). This study also reported that the reinstatement of a conditioned place preference was blocked by a selective orexin-1 receptor (Ox1R) antagonist, thus demonstrating a causal role for signaling at this specific receptor in the regulation of drug seeking (Harris et al., 2005). In the almost two decades since, these original findings have been recapitulated across multiple experimental paradigms, species of laboratory animals, as well as classes of drugs. Indeed, across all misused substances tested (including cocaine, opioids, nicotine, alcohol), Ox1R antagonists are effective at reducing ‘relapse’ elicited by drug-associated stimuli/contexts and stress in animals (Mahler et al., 2014; James et al., 2017; Mehr et al., 2021; Mahler et al., 2012), in part via actions at VTA (Pantazis et al., 2021; James et al., 2011; Mahler et al., 2013; Wang et al., 2009; Espana et al., 2011). Moreover, these agents generally reduce high-effort responding for all drugs on progressive ratio and behavioral economics procedures without affecting low-effort self-administration intake (Fragale et al., 2019; James et al., 2019a; James et al., 2019b; Mohammadkhani et al., 2019a; Mohammadkhani et al., 2019b), pointing to a unique role for the Ox1R system in regulating the motivational, but not the hedonic, properties of drugs of abuse (James et al., 2017; James and Aston-Jones, 2022a). These effects are particularly pronounced in animals with high baseline drug motivation (James et al., 2019a; Moorman et al., 2017). Interestingly, more orexin immunoreactive neurons are observed in the hypothalamus of animals and humans with a history of drug use (James et al., 2019b; James and Aston-Jones, 2022a; Thannickal et al., 2018; Collier et al., 2019; Collier et al., 2021; Fragale et al., 2020), and animals with higher numbers of endogenous orexin neurons are more prone to exhibiting an addiction-like phenotype (Pantazis et al., 2019). Thus, a higher number of orexin neurons (attributed to the recruitment of a ‘reserve’ pool of orexin neurons) appears to be a common ‘neuronal fingerprint’ for the manifestation of addiction (James and Aston-Jones, 2022a) (cf. no change or fewer orexin neurons following chronic alcohol exposure (McGregor et al., 2023)). Thus, strategies to reduce orexin signaling

(including orexin receptor antagonism) might be protective against drug seeking and craving for all drug classes (James and Aston-Jones, 2022b).

In addition to their role in reward, the orexin neurons play a fundamental role in stabilizing wakefulness (Tyree et al., 2018). This is perhaps most dramatically illustrated by the fact that persons with narcolepsy, a neurological disorder characterized by excessive daytime sleepiness, are almost entirely deficient in orexin (~80% reduction in orexin neurons) (Thannickal et al., 2000). Orexin neurons exhibit a diurnal pattern of activity and peptide production, characterized by high signaling during the active period and low levels during the inactive period (McGregor et al., 2017; Estabrooke et al., 2001; Mileykovskiy et al., 2005). Orexins exert their wake-promoting effects via direct actions at arousal-promoting cell groups, including at locus coeruleus noradrenergic neurons, histamine neurons in tuberomammillary nucleus, and cholinergic neurons in the brainstem and basal forebrain (Liu et al., 2002; Hagan et al., 1999; Eriksson et al., 2001; Burlet et al., 2002). Accordingly, stimulation of orexin neurons generally increases overall wakefulness and suppresses both NREM and REM sleep, whereas inhibition of orexin neurons has the opposite effect (Sasaki et al., 2011; Adamantidis et al., 2007; Li et al., 2022). In contrast to reward processes, the pro-wakefulness effects of orexin signaling are largely mediated via actions at the Ox2R; however, simultaneous blockade of both Ox1R and Ox2R promotes sleep more effectively compared to an Ox2R antagonist alone (Morairty et al., 2012). Considering these outcomes, three dual Ox1R/Ox2R antagonists have been developed and have gained approval for the treatment of insomnia (in non-SUD populations) (Wu et al., 2022). Suvorexant, marketed as Belsomra (Merck), was the first to gain FDA approval, and has been studied most extensively (Cox et al., 2010); suvorexant reduces time to sleep onset, increases total sleep time, and maintains normal sleep architecture (Coleman et al., 2017). The other approved compounds include lemborexant (Dayvigo, Eisai) and daridorexant (Quvivic, Idorsia), which also generally improve sleep outcomes.

There has been a recent swell of interest in the potential application of Ox1R and Ox1R/Ox2R antagonists in SUD populations, with the former expected to directly reduce cravings and relapse (i.e., without promoting sedation), whereas the latter might indirectly reduce the risk of return to use by improving sleep outcomes during abstinence (Morgan and Malison, 2007; James et al., 2020; Fragale et al., 2021; Huhn et al., 2022; Reid et al., 2024). At present, no selective Ox1R antagonists have gained FDA approval, however there are several in development, including two being developed specifically for the treatment of OUD (INDV-2000, Indivior; AZD4041, AstraZeneca), which have both completed Phase 1 trials (results not yet disclosed). Other Ox1R antagonists, including CVN766 (Cerevance), which are being developed for alternative indications (e.g. schizophrenia), may be candidates for repurposing in SUD populations if/when they gain FDA approval. In addition, artificial intelligence/machine learning approaches have been utilized to identify existing compounds with actions at the Ox1R that may be suitable for repurposing, with some success (Zhang et al., 2024).

In the absence of clinically available Ox1R antagonists, the limited number of exploratory studies testing orexin compounds in SUD patients have exclusively utilized the clinically available dual Ox1R/Ox2R antagonists. The first such study was published in 2020, in

which suvorexant (dosed in the evening; vs. placebo control) tended to reduce several relapse-related factors in CUD patients, including attentional bias toward drug stimuli, insomnia, and heart rate reactivity to stress and craving (Suchting et al., 2019). Although promising, these data were limited by the exploratory nature of the study (n = 10 per treatment group). In a landmark study published several years later, the effects of suvorexant were tested in OUD patients undergoing a 4-day buprenorphine/naloxone taper (Huhn et al., 2022). Suvorexant treatment was associated with increased total sleep time during the taper period, as well as reductions in several indices of opioid craving during both the taper and post-taper periods (Huhn et al., 2022). These authors subsequently reported that suvorexant-induced reductions in craving were associated with specific sleep-EEG band power changes, indicating a potential causal link between the two outcomes (Reid et al., 2024). The mechanistic link between improved sleep and reduced craving following suvorexant treatment has not been well characterized, but might reflect improved executive function ('top down' control), direct inhibition of reward centers involved in craving ('bottom up' control), or a combination of the two (Gyawali and James, 2023). Curiously, two recent studies reported that suvorexant maintenance (dosed in the evening over 3 days) was associated with an *increase* in self-administration of a fixed dose of intravenous cocaine, as well as cocaine demand, in a small (n = 7–8) number of cocaine use disorder patients (Stoops et al., 2022; Strickland et al., 2023). The reasons for these discrepant outcomes are unclear, however it is worth noting that patients in these studies were non-treatment seeking (unlike in the buprenorphine/naloxone taper study) and thus were active cocaine users. These initial studies have fueled enthusiasm for exploring the potential repurposing of dual orexin receptor antagonists in SUD populations. Currently, there are several ongoing clinical trials examining the utility of these compounds for improving sleep and related craving outcomes for NUD, AUD, and OUD, as well as in persons with comorbid opioid and stimulant use (NCT05546515).

It is worth noting that although dual Ox1R/Ox2R receptor antagonists are used to promote sleep, limited preclinical evidence indicates that these same compounds might have utility at lower doses to reduce craving (without affecting arousal) during the day. For example, acute treatment with suvorexant during the active period decreased motivation for fentanyl (O'Connor et al., 2020) and cocaine (Gentile et al., 2017a), and reduced cocaine-induced impulsive behaviors (Gentile et al., 2017b), at doses that did not produce sedation or impairment (also see Wiskerke et al., 2020 for evidence that selective Ox1R antagonists do not impair cognition at doses that reduce drug seeking). Clinical use of dual orexin receptor antagonists during the daytime will be challenging from a regulatory perspective, given their classification as a hypnotic agent, further highlighting the urgent need for the development and approval of selective Ox1R antagonists for managing craving and drug-directed behaviors during the daytime.

8. Oxytocin and oxytocin receptor agonists to reduce drug craving and intake

Oxytocin (OXT) is a neuropeptide produced in the hypothalamus, which has dense projections to regions within the limbic system, basal ganglia, and forebrain, overlapping

substantially with the neurocircuitry involved in the development and maintenance of SUDs (Knobloch et al., 2012; Koob and Volkow, 2010). The Gq-coupled oxytocin receptor (OXTR) is expressed throughout similar structures, and via agonism of the OXTR at nanomolar concentrations, OXT exerts control over a variety of affective, cognitive, and behavioral processes relevant to SUDs (Jurek and Neumann, 2018). Chronic exposure to addictive drugs in both humans and animals is known to cause dysregulation of the OXT system, reflected in decreased numbers of OXT neurons and altered OXTR expression (Che et al., 2021). Additionally, clinical studies have revealed an association between OXT levels in the blood with behavioral and mood outcomes during heroin withdrawal (Nikolaou et al., 2017) and alcohol consumption with OXT and OXTR mRNA levels in post-mortem human brain tissue (Lee et al., 2017). This link between endogenous OXT/OXTR expression and addiction-related outcomes in humans is mirrored by preclinical evidence across various classes of drugs of abuse. For example, in rats, hypothalamic OXT peptide expression correlates with behavioral economic demand for heroin (Giannotti et al., 2022), and chronic methamphetamine self-administration reduces OXTR expression in the NAc and subthalamic nucleus (Baracz et al., 2016a). Together, this suggests that the endogenous OXT system is impacted by substance use, its expression is correlated with addiction-related function, and that it is well-positioned to influence addiction-related outcomes. This has strengthened the hypothesis that addiction symptoms may be reduced by enhancing OXT signaling through exogenous administration with OXT or novel OXTR agonists.

There is now substantial preclinical data that for multiple drugs of abuse, at various stages of the addiction cycle, administration with OXT may be therapeutic. There are numerous reviews synthesizing these preclinical datasets across substance classes (Bowen and Neumann, 2017), so here we briefly highlight some of these studies, which give insight into translational mechanisms of action and enduring efficacy in models of drug taking and seeking. For example, acute systemic OXT administration dose-dependently reduces intake of methamphetamine (Carson et al., 2010), cocaine (Bentzley et al., 2014; Zhou et al., 2015), alcohol (MacFadyen et al., 2016), and heroin (Kovács et al., 1985). The effects of OXT treatment also appear to depend upon the addiction-like phenotype of the subject, as OXT treatment has larger effects on cue-induced reinstatement of methamphetamine-seeking in rats that display sign-tracker-like behavior (Everett et al., 2020a) and higher baseline motivation for cocaine (Bentzley et al., 2014). Some of the most promising preclinical datasets are those that utilize chronic OXT treatment and have demonstrated protective effects, which endure far beyond the pharmacokinetics of OXT. For example, chronic OXT treatment in adolescent rats reduces consumption of alcohol (Bowen et al., 2011) and self-administration of methamphetamine (Hicks et al., 2016) into adulthood. Although such pre-treatment studies may be challenging to translate clinically, other studies have explored chronic OXT as a post-treatment after chronic stress or drug exposure. Specifically, chronic OXT treatment during abstinence from methamphetamine self-administration produced an enduring reduction in cue, drug, and stress-induced reinstatement of methamphetamine-seeking behaviors, only in rats which had a history of extended—but not short access—to methamphetamine (Everett et al., 2020b). Similarly, chronic OXT treatment protected against elevated reinstatement of methamphetamine-

seeking induced by predator odor exposure in rats (Ferland et al., 2016), chronic OXT treatment during abstinence from experimenter-administered methamphetamine protected against the reinstatement of methamphetamine conditioned place preference in mice (Cai et al., 2022), and chronic OXT treatment during adolescence in rats protected against increased methamphetamine-seeking behaviors in adulthood induced by early life stress in rats (Baracz et al., 2022). Together, these datasets suggest that acute OXT administration can suppress drug-taking and -seeking behaviors, and that chronic OXT treatment may elicit neurobiological changes, which interact with stress and addiction neurobiology, permitting long-lasting therapeutic effects.

The neurobiology of OXT's effects in rodent addiction models has been well-studied, and collectively implicates various meso-corticolimbic-striatal structures critically involved in addiction processes, as regions where OXT causally acts to reduce drug behaviors. For example, in a behavioral economics model of methamphetamine demand, both systemic oxytocin and oxytocin micro-infusion into the NAc core decreased methamphetamine demand, as well as cue-induced reinstatement (Cox et al., 2017), and methamphetamine-primed reinstatement (Baracz et al., 2016b) of extinguished drug-seeking behavior. Notably, the effects of systemic OXT administration on methamphetamine self-administration were prevented by OXTR antagonism in the NAc (Cox et al., 2017), although OXT effects on suppressing reinstatement may also involve vasopressin V_1A receptor activity (Everett et al., 2018). This central site of action of OXT for reducing addiction symptoms is further supported by rodent alcohol self-administration studies, whereby intracerebroventricular but not intraperitoneal administration with a non-blood-brain-barrier-penetrant OXTR antagonist prevented peripherally administered oxytocin from reducing alcohol consumption (Tunstall et al., 2019). Microinjection studies have also identified the prelimbic cortex (Everett et al., 2019) and subthalamic nucleus (Baracz et al., 2015) as sites where OXT can act to reduce reinstatement of methamphetamine-seeking behaviors in rats, and histological analyses have correlated changes to hippocampal neurogenesis with the enduring effects of OXT in methamphetamine addiction models (Cai et al., 2022). Some of these preclinical neurobiological findings are supported by clinical neuroimaging studies, which, for example, have identified that intranasal OXT administration in social alcohol drinkers can suppress the functional connectivity of the NAc, specifically in response to alcohol cues (Bach et al., 2019). Similarly, intranasal OXT reduced cocaine-cue elicited fMRI activity in the dorsomedial prefrontal cortex of cocaine-dependent people, an effect which also occurred in the amygdala of men but not women who had a history of childhood trauma (Joseph et al., 2019). Overall, there is compelling and convergent preclinical and clinical evidence that exogenous OXT, likely via OXTR agonism, can acutely and chronically modulate signaling in addiction-relevant neural pathways.

Following this promising preclinical data, and the relative ease by which OXT can be sourced and safely administered to people, there have been numerous clinical trials investigating OXT as a therapeutic for substance use disorders. Others have reviewed these RCTs in depth (Mellentin et al., 2023), which involve people with AUD, StUD, MUD, OUD, NUD, or CaUD, and which involve measures of craving, tolerance, withdrawal, drug consumption, and social and emotional functioning. Collectively, there is some evidence that intranasal OXT treatment may reduce withdrawal symptoms, negative affect,

spontaneous cravings, cue-elicited cravings, and drug consumption (Mellentin et al., 2023). However, these findings are often inconsistent between studies, possibly due to differences in treatment stage, co-occurring psychological interventions, OXT dosage, intranasal administration method, patient history of early life trauma, and insufficient statistical power. Each of these factors can and should be considered in future clinical trials, which may slightly improve confidence or understanding of the potential clinical usage of OXT. However, iteratively improved clinical trial design is unlikely to overcome the fundamental limitation of the poor developability of oxytocin as a pharmacotherapeutic.

The physiochemical properties of the OXT peptide make it unsuitable for clinical usage; in terms of pharmacokinetics, OXT is rapidly degraded by peptidases in the gastrointestinal tract (Hamman et al., 2005) and consequently cannot be orally administered, and when administered via other peripheral routes, its plasma half-life is ~5 minutes (Morin et al., 2008). Consequently, approximately only 0.003% of the administered peripheral dose is detectable in the cerebrospinal fluid 10 min after injection (Mens et al., 1983). As for pharmacodynamics, OXT exhibits adverse effects at vasopressin receptors, as both OXT and vasopressin are cyclic nonapeptides differing at only two amino acid positions (Postina et al., 1996), with significant structural homology between their respective receptors (Gimpl and Fahrenholz, 2001), which are typically anti-targets for drug development. Moreover, binding of OXT to its receptor, a class I G-protein coupled receptor, results in rapid internalization and receptor desensitization, reducing the efficacy of subsequent OXT exposures (Smith et al., 2006). These factors are likely precluding the field from testing the clinical hypothesis of OXTR agonism sufficiently, and are unlikely to be overcome by nanoparticle formulations (for example), or marginally optimized intranasal administration methods (Leng and Ludwig, 2016), which do not address these substantial limitations inherent to the OXT peptide. Despite this, there is reason for optimism that oxytocin may yet emerge as an addiction therapeutic.

For the therapeutic potential of OXTR agonism to be rigorously tested in the clinic, there is a need for OXTR agonists and/or allosteric modulators with better drug-like properties than the OXT peptide, including greater selectivity for OXTR over vasopressin receptors, improved brain penetrance and metabolic stability, and longer duration of action. Several research groups are actively developing such compounds, mostly within the context of social behavior, with the aim of introducing them into the clinic within the next few years. One such compound—LIT-001—has been developed by the University of Strasbourg as a non-peptide OXTR agonist, which exhibits a longer half-life and greater blood-brain barrier permeability than oxytocin and promotes social interaction in a mouse model of autism spectrum disorder (Frantz et al., 2018). With respect to its potential utility as an addiction therapeutic, LIT-001 administration reduced voluntary alcohol consumption for up to 6 h after acute treatment in male prairie voles (Potretzke et al., 2023), suggesting that the anti-addiction effects of oxytocin can be retained by compounds that are very structurally distinct from the endogenous peptide, but retain activity at OXTR. LIT-001 also produces OXTR-dependent analgesia in rats (Hilfiger et al., 2020), which may be beneficial for eventual use in SUDs patients with comorbid pain, such as in the case of OUD. Despite this impressive progress, LIT-001 and its analogues are still in preclinical development, possibly owing to their poor functional selectivity, as they have activity at vasopressin receptors,

which may affect renal function. Small molecule OXTR-targeting compounds are also being developed by a partnership between Kinoxis Therapeutics (a spin-out from the University of Sydney) and Boehringer Ingelheim, announced in 2023 (note that several authors on the current manuscript are affiliated with Kinoxis Therapeutics) (Lowe, n.d.). Although data from these compounds have not yet been published, the partnership is reportedly focused on developing OXTR-targeting therapeutics for disrupted social behavior. Notably, if the compounds are successful clinically, this indication approach may benefit people with SUD diagnoses who exhibit disrupted social behavior, even if not being developed for SUDs explicitly. Finally, there is ongoing exploration of a peripherally restricted OXTR agonist, ASK1476, originally published under the name PF1 by Pfizer, and its analogues. ASK1476 demonstrates enhanced selectivity for the OXTR, greater plasma stability (Modi et al., 2016), and OXT-like effects on anxiety-like behaviors and obesity (Elfers et al., 2021). As this compound lacks brain penetrance, its effects are presumed to result from peripheral OXTR binding, which may include vagal OXTRs which are causally implicated in the suppressing effects of oxytocin treatment on food intake in mice (Iwasaki et al., 2019) and methamphetamine self-administration in rats (Everett et al., 2021).

Together this suggests that peripheral OXTR agonism, without vasopressin receptor activity, may offer an additional avenue for clinical development of OXTR-targeting compounds. Overall, the oxytocin field eagerly awaits the clinical testing of one or more of these selective OXTR agonists with improved drug-like properties to sufficiently test the hypothesis that OXTR agonism could be therapeutic for SUDs.

9. Concluding remarks

As previously noted, pharmaceutical companies have historically had low enthusiasm for investing in the development of SUD medications. This has been attributed to a confluence of factors, including stigma toward SUD as a medical disorder, challenges associated with recruiting for, and conducting, clinical trials, as well as a lack of standards regarding clinical trials designs and outcomes (Montoya and Volkow, 2024). Recognizing these challenges, government agencies including the National Institutes of Drug Abuse have made substantial investments in advancing our understanding of the neurobiology of SUDs, as well as the subsequent development of new medications and their testing. As is outlined in this review, there are currently many promising, novel opportunities in the development pipeline. Thus, notwithstanding the ongoing headwinds for SUD medication development, there is reason for optimism that novel pharmacotherapies specifically designed to treat the unique and multifaceted symptomology of SUDs will become available in the near future.

Funding sources

This work was funded by grants to MTB from the Australian National Health and Medical Research Council (1092046, 1166044), NAE from the Australian National Health and Medical Research Council (2027034), and to MHJ from the National Institute on Drug Abuse (R00 DA04765, R37 DA061303), the National Heart Lung and Blood Institute (U01HL 150852), Rutgers Optimizes Innovation, and the New Jersey Health Foundation (PC144-23 and PC98-22).

Declaration of interests

MHJ is an inventor on patent application PCT/US23/27918, and provisional patent applications US 63/601,522, and US 63/702,018 which describe novel treatments for psychiatric illnesses, including substance use disorders. In addition to his academic role, MTB is co-founder and Chief Scientific Officer of Kinoxis Therapeutics Pty Ltd., an Australian-based company developing novel small molecule treatments for brain disorders, including the treatment of substance use disorders and social impairments in psychiatric conditions. In addition to his academic role, NAE is Head of Behavioral Neuroscience at Kinoxis Therapeutics, and Head of Behavioral Pharmacology at Psylo Pty Ltd. MTB and NAE receive research funding from Kinoxis Therapeutics, and NAE receives research funding from Psylo. RS is an employee of Kinoxis Therapeutics. The work presented in this manuscript is unrelated to RE's, MTB's and NAE's role with Kinoxis Therapeutics, or NAE's role with Psylo. All other authors declare no conflicts of interest.

Data availability

No data was used for the research described in the article.

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Table 1

Emerging medications and pharmacological treatment approaches for substance use disorders in ongoing clinical trials.

Treatment approaches and pharmacological targets	SUD class	Medication(s)	Clinical endpoints of interest	SUD clinical trials
Psychostimulant-based agonist therapy	StUDs; CoUD and MUD	Dextroamphetamine formulations	Abstinence Stimulant use Craving	[CUD[a]] NCT05529927
		Lisdexamfetamine	Abstinence Stimulant use Craving	[MUD] ACTRN12617000657325; NCT05854667
Psychedelics and $5HT_{2A}R$ modulation	AUD, CaUD, MUD, NUD, OUD	DMT	Alcohol use Intention to drink alcohol	[AUD] NCT06070649
		Psilocybin	Abstinence Craving Drug use Withdrawal Return to use	[AUD] NCT06405607; NCT06235411; NCT06349083; [CaUD] NCT06660381; NCT06225232; [MUD] NCT04982796; [NUD] NCT05452772; [OUD] NCT04161066; NCT06160284; NCT06067737
GLP-1 receptor agonism	AUD, CoUD, NUD, and OUD	Exenatide	Drug use Subjective effects of cocaine	[CoUD] NCT04941521; NCT06252623
		Liraglutide	Abstinence	[AUD] NCT06546384; [NUD] NCT03712098; [OUD]
			Cue-induced craving	NCT04199728
		Semaglutide	Abstinence	[AUD] NCT06015893; NCT05891587; [OUD] NCT06548490;
			Change in drug use	[NUD] NCT05530577
Cannabidiol and related cannabinoid receptor modulation	AUD, CaUD, CoUD, NUD, and OUD	Cannabidiol	Abstinence Craving (ambient and cueinduced) Change in drug use Drug cue-induced anxiety Reduction in pain and pain medication use	[AUD] NCT05613608; NCT05159830; NCT06512389; NCT05860699; NCT05387148; NCT05317546; NCT04873453; [CaUD] ACTRN12623000526673; [CoUD] NCT02559167; NCT06159387; [NUD] NCT06218056; NCT05445804; [OUD] NCT06206291, NCT05299944, NCT04587791, NCT04587791
	CaUD	AEF0117	Cannabis use Subjective positive experience of cannabis use	NCT05322941; NCT03717272, NCT03325595, NCT03443895
Kappa opioid receptor antagonism	AUD and OUD	Aticaprant CVL-354	Experience of negative affect during withdrawal[b]	No trials in SUD populations yet
Orexin (hypocretin) receptor antagonism	AUD, NUD, and OUD	Suvorexant	Craving Drug cue reactivity Drug use-related stress Drug use-related sleep disturbances Subjective positive experience of drug use Withdrawal	[AUD] NCT06326684; NCT05656534; NCT06484075; [CoUD] [NUD] NCT05630781; NCT03999099; [OUD] NCT05145764; NCT04287062; NCT06655883; NCT05829655
		Lemborexant	Craving (cued and non-cued) Drug use-related sleep disturbances	[AUD] NCT05458609; [OUD] NCT04818086
		Daridorexant	–	No trials in SUD populations yet

Treatment approaches and pharmacological targets	SUD class	Medication(s)	Clinical endpoints of interest	SUD clinical trials
Oxytocin and oxytocin receptor agonism	AUD, CaUD, CoUD, MUD, NUD, and OUD	Oxytocin peptide	Change in drug use Craving Drug-related stress and anxiety Impulsivity Withdrawal and negative affect	[AUD] NCT06199076; NCT04523922; NCT06224127; [CoUD] NCT02028533; NCT02682784; [NUD] NCT02595749; [OUD] NCT04051619
	–	LIT-001	–	No trials in SUD populations yet
	–	ASK1476	–	No trials in SUD populations yet

Abbreviations: AUD – alcohol use disorder; CaUD – cannabis use disorder; CoUD – cocaine use disorder; DMT – *N*, *N*-dimethyltryptamine; MUD – methamphetamine use disorder; StUDs – stimulant use disorders; SUD – substance use disorder.

[a] Comorbid OUD;

[b] Based on preclinical data. Note that clinical trial examples are non-exhaustive.