Current Perspectives on Selective Dopamine D_3 Receptor Antagonists/Partial Agonists as Pharmacotherapeutics for Opioid and Psychostimulant Use Disorders

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Abstract Over three decades of evidence indicate that dopamine (DA) D_3 receptors (D_3R) are involved in the control of drug-seeking behavior and may play an important role in the pathophysiology of substance use disorders (SUD). The expectation that a selective D_3R antagonist/partial agonist would be efficacious for the treatment of SUD is based on the following key observations. First, D_3R are distributed in strategic areas belonging to the mesolimbic DA system such as the ventral striatum, midbrain, and ventral pallidum, which have been associated with behaviors controlled by the presentation of drug-associated cues. Second, repeated exposure to drugs of abuse produces neuroadaptations in the D_3R system. Third, the synthesis and characterization of highly potent and selective D_3R antagonists/partial agonists have further strengthened the role of the D_3R in SUD. Based on extensive preclinical and preliminary clinical evidence, the D_3R shows promise as a target for the development of pharmacotherapies for SUD as reflected by their potential to (1) regulate the motivation to self-administer drugs and (2) disrupt the responsiveness to drug-associated stimuli that play a key role in reinstatement of drug-seeking behavior triggered by re-exposure to the drug itself, drug-associated environmental cues, or stress. The availability of PET ligands to assess clinically relevant receptor occupancy by selective D_3R antagonists/partial agonists, the definition of reliable dosing, and the prospect of using human laboratory models may further guide the design of clinical proof of concept studies. Pivotal clinical trials for more rapid progression of this target toward regulatory approval are urgently required. Finally, the discovery that highly selective D_3R antagonists, such as *R*-VK4-116 and *R*-VK4-40, do not adversely affect peripheral biometrics or cardiovascular effects alone or in the presence of oxycodone or cocaine suggests that this class of drugs has great potential in safely treating psychostimulant and/or opioid use disorders.

Keywords D3 receptor antagonist · D3 receptor partial agonist · Dopamine · Opioids · Psychostimulants · Substance use disorders

1 Introduction: Brief Historical Perspective/Epidemiology

> Meteorologists see perfect in strange things, and the meshing of three completely independent weather systems to form a hundred-year event is one of them. My God, thought Case, this is the perfect storm.
>
> — Sebastian Junger, The Perfect Storm: A True Story of Men Against the Sea

1.1 The Perfect Storm

The COVID-19 pandemic has brought our world to its knees in a way that most of us never imagined. The SARS-CoV-2 virus has managed to infect and mutate, becoming more virulent over time, resulting in death and destruction of economies,

livelihoods, and a way of life that no one could have predicted. While massive resources and biomedical research focused on vaccines and medications to save lives, two other crises were brewing. The opioid epidemic was just starting to see the beginning of a downward trend, at least in terms of death by overdose (Ahmad et al. 2021). And although the use of psychostimulants such as cocaine and methamphetamine was still a relevant health assailant, it had not yet reached the point of crisis. Nevertheless, the devastation, isolation, hopelessness, and fatigue brought on by the COVID-19 pandemic have exacerbated substance misuse, joining forces to reverse the upward trend of life longevity in the USA (Manchikanti et al. 2021) and resulting in >90,000 drug overdose deaths, an increase of >30% in 2020 over the year before (Ahmad et al. 2021; Volkow 2021). The decrease in health services, limited access to medical care, and increased access to highly potent opioids such as fentanyl, etonitazene, and their illicit analogues have been complemented by an increased supply of methamphetamine, the combinations of which were more deadly than either one alone or sometimes ingested without the user's knowledge (Narayan and Balkrishnan 2021).

The challenges that the COVID-19 epidemic introduced to mental health cannot be underestimated. Isolation-related anxiety and depression are among the disorders that have increased and been exacerbated. Closely coupled to these is the management of pain, which has also been impaired by lack of access to medical care and is the leading reason patients take prescription opioids that for some can lead to dependence or addiction (Kibaly et al. 2021; Taquet et al. 2021a, b). Sheltering in place and restrictions in travel have impacted patients' ability to obtain proper medical care and necessary medications. Patients in chronic pain become depressed and the vicious cycle is unrelenting, unless acutely mitigated by the use of illicit drugs – a solution that has devastating consequences.

People with substance use disorders (SUD) are at heightened risk for other life-threatening comorbidities including cardiovascular disease, mucociliary dysfunction, compromised immunity as well as multiple social factors that prevent proper treatment (Manchikanti et al. 2021). And indeed, those whose prescription opioid taking accelerates to illicit drug use and addiction, only enhances their chances of becoming infected with SARS-CoV-2 and succumbing to the virus, overdose, or both. Sadly, as with other crises, underserved populations receive the disproportionate impact of this trifecta of tragedy (Narayan and Balkrishnan 2021).

1.2 Opioid Crisis

By 2019, the opioid epidemic in the USA was noted as a health crisis that was continuing to escalate (Lyden and Binswanger 2019). Although illicit opioids such as heroin had been contributing to opioid-related deaths for decades before, the increase in prescribed opioids for the management of pain, and especially the over prescription of extended-release formulations of oxycodone (e.g., oxycontin) significantly escalated opioid dependence and addiction in the USA. As oxycontin was

first marketed as less addictive than other opioid narcotics, a dramatic increase in its use for pain management ultimately resulted in escalated opioid overdoses in the last decade (Azadfard et al. 2021; Kibaly et al. 2021; Walker 2018). According to the Centers for Disease Control and Prevention (CDC), 96,779 people died from drug overdose in the 12-month period ending March 2021. Approximately 72,805 of these deaths were attributed to all opioids, and 61,230 were attributed to synthetic opioids such as fentanyl (Ahmad et al. 2021).

Studies that attempt to quantify the burden of opioid-related mortality conclude that premature deaths caused by opioid overdose has and undoubtedly will continue to impose an enormous health and economic burden on the USA (Gomes et al. 2018). In 2016, years of life lost (YLL) exceeded those attributed to hypertension, HIV, and pneumonia (Gomes et al. 2018). Sadly, 25–34 years of age was the demographic with the highest opioid overdose death rate. Young adults who had the potential to contribute so much to our society and may have left children behind – yet another tragic reality.

1.3 Psychostimulant Use Disorder: Cocaine and Methamphetamine

As if the COVID-19 pandemic and the opioid crisis were not enough to keep researchers and health care providers, legislators, and parents up at night, a new wave of drug abuse is now rolling through our cities and rural areas alike. Although cocaine continues to be a drug of high abuse potential and related death by overdose, methamphetamine has roared into our streets and communities (Compton et al. 2021; Fogger 2019; Jones et al. 2020). Methamphetamine is easily synthesized in home laboratories, has a longer half-life than cocaine, and is more easily accessible, likely contributing to its added popularity, which has increased during the COVID-19 pandemic.

1.4 Polysubstance Use Highlighting Opioids/Methamphetamine

The "old practice" of combining heroin with cocaine known as "speedball" has been replaced with the combination of methamphetamine and heroin or fentanyl, called "goofball" (Glick et al. 2021) with grave consequences. Some users of this combination of drugs claim that the addition of methamphetamine to the opioid reduces unpleasant sluggishness/lethargy and the opioid decreases the unpleasant intensity of methamphetamine (Ciccarone 2021; Glick et al. 2021). Clearly polysubstance use is prevalent and highly complex, leading to an increase in morbidity and poses further challenges for prevention and treatment. Although a decline in overdose deaths

appeared in 2017–2018, the CDC reports an increased mortality that is alarming, driven by a dramatic increase in opioid-related deaths and now a "fourth wave" of high mortality involving cocaine and primarily methamphetamine (Ciccarone 2021).

1.5 Co-Morbidities with Other Neuropsychiatric Disorders

In addition to polysubstance use, prevailing public health problems that have been exacerbated by the COVID-19 pandemic are psychiatric disorders, including anxiety, major depressive disorder, and bipolar disorder. These disorders are complex and often difficult to treat. Equally alarming is the comorbidity between these disorders and SUD, a public health concern that emerged long before COVID-19 but has undoubtedly increased (Angarita et al. 2021a; Hellem et al. 2015; Murthy et al. 2019).

2 D_3R Neurocircuitry and Relationship to SUD

2.1 Rationale of D_3R-Based Medication Development for the Treatment of Psychostimulant and Opioid Use Disorders

2.1.1 Dopamine Hypothesis of Drug Reward

It is well documented that the mesolimbic and nigrostriatal dopamine (DA) systems are critically involved in psychostimulant and opioid reward (Galaj and Xi 2021; Lammel et al. 2014) (Fig. 1). These systems originate from DA neurons in the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) in the midbrain and project to the nucleus accumbens (NAc), dorsal striatum (DST), ventral pallidum (VP), prefrontal cortex (PFC) and insula, as well as the amygdala (Amy). A great deal of evidence supports the importance of both the DA projection pathways in SUD. First, almost all addictive drugs, including cocaine, opioids, nicotine, and ethanol, increase extracellular DA in the NAc and DST (Koob and Bloom 1988; Self and Nestler 1995). Second, almost all addictive drugs can be self-administered by animals either intravenously or locally into the VTA or NAc, which can be blocked or attenuated by either chemical lesions of DA terminals or by pharmacological blockade of DA receptors (Bressan and Crippa 2005; Gardner 2000). And third, electrical or optical stimulation of brain DA loci maintains intracranial self-administration, which can be enhanced by drugs of abuse and attenuated by DA receptor antagonists (Wise 1996).

Psychostimulants and opioids activate the mesolimbic and nigrostriatal DA systems by different molecular and cellular mechanisms. Cocaine elevates extracellular DA levels in the DA projection areas mainly by blockade of DA reuptake,

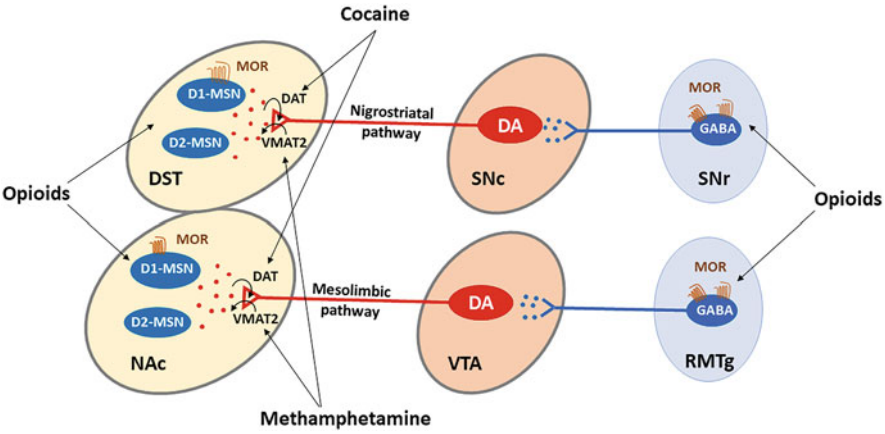

Fig. 1 Schematic diagram of the mesolimbic and nigrostriatal reward pathways, illustrating the action sites (targets) of psychostimulants (cocaine, methamphetamine) and opioids in the brain. The mesolimbic DA circuit (RMTg → VTA → NAc) originates in the midbrain ventral tegmental area (VTA) and projects predominantly to the nucleus accumbens (NAc) and other forebrain regions (not shown). VTA DA neurons receive GABAergic inputs from local VTA GABA neurons and other brain regions including the NAc, ventral pallidum (VP), and rostromedial tegmental nucleus (RMTg), particularly from the RMTg. Psychostimulants elevate extracellular NAc DA by blocking DA transporters (DAT) (by cocaine) or reversing VMAT2 (by methamphetamine) on DA axon terminals in the NAc and dorsal striatum (DST). The nigrostriatal DA circuit (SNr → SNc → DST) originates from DA neurons in the substantia nigra pars compacta (SNc) and projects to the DST. SNc DA neurons receive dense GABAergic inputs from multiple brain regions including the SNr and RMTg, but mainly from SNr. Mu opioid receptors (MOR) are highly expressed in GABA neurons, particularly in the RMTg and SNr. Opioids bind to MORs and inhibit GABA neuron activity and GABA release, which subsequently disinhibits DA neurons in the VTA and SNc

while amphetamine or methamphetamine mainly promotes DA release from DA terminals by reversal of vesicular monoamine transporter 2 (VMAT2), which promotes DA exit from vesicles into cytoplasm and causes DA release from cytoplasm to extracellular space by reversal of membrane dopamine transporter (DAT) (Elkashef et al. 2008; Freyberg et al. 2016; Shen et al. 2021) (Fig. 1). These increases in synaptic or extracellular DA in the forebrain reward loci – especially in the NAc – are thought to underlie the euphoria associated with psychostimulant use (Wise 2005).

In contrast to psychostimulant reward, the neural mechanisms underlying opioid reward and abuse are still not fully understood. A classical hypothesis is that opioids initially bind to mu opioid receptors (MOR) located on GABAergic interneurons within the VTA and functionally inhibit GABAergic neuronal activity, which subsequently disinhibits neighboring DA neurons within the VTA (Galaj and Xi 2021; Xi and Stein 2002). This canonical two-neuron hypothesis, which was upheld for over half a century, has been challenged by recent findings suggesting that high density MORs are expressed in GABAergic neurons mainly in the rostromedial

tegmental nucleus (RMTg, also called the tail of the VTA) and substantia nigra pars reticulata (SNr) in the midbrain (Galaj et al. 2020a; Galaj and Xi 2021; Matsui et al. 2014; Matsui and Williams 2011). It has been shown that DA neurons in the VTA and SNc receive intensive GABAergic inputs mainly from the RMTg and the SNr, respectively (Galaj et al. 2020a; Matsui and Williams 2011), suggesting that DA neurons in the VTA and SNc may be activated mainly by activation of MORs in GABAergic neurons in both the RMTg and SNr via a disinhibition mechanism. Thus, a two-pathway hypothesis (e.g., RTMg → VTA → NAc, SNr → SNc → DST) has been proposed to explain opioid reward and abuse (Fig. 1) (Galaj et al. 2020a; Galaj and Xi 2021).

Based on this DA hypothesis, one strategy to manipulate the downstream DA transmission in the brain reward circuitry is to target (block) DA receptors (D_1, D_2, D_3, D_4) for the treatment of SUD and another is to target the DAT specifically for the treatment of psychostimulant use disorder (PSUD) (Newman et al. 2021). The D_3R is a major focus in the former strategy (Galaj et al. 2020b), which will be addressed extensively below, while developing various DAT inhibitors, particularly atypical DAT inhibitors, is the major focus in the latter strategy, which has recently been reviewed extensively elsewhere (Hersey et al. 2021; Tanda et al. 2021).

2.1.2 Unique Profiles of D_3R

There are five G protein-coupled DA receptor subtypes identified, which are classified into D_1-like (D_1, D_5) and D_2-like (D_2, D_3, D_4) groups based on their homology, pharmacology, and intracellular signaling properties (Beaulieu et al. 2015; Beaulieu and Gainetdinov 2011; Martel and Gatti McArthur 2020; Missale et al. 1998). The D_1 and D_5 receptors share 80% homology of their seven transmembrane domains, while the D_2 receptors share 75% homology of their protein structure with D_3R and only 53% homology with D_4 receptors. The main structural differences among DA receptors are differences in size of the third intracellular loop connecting transmembrane domains and of the carboxyl-terminal intracellular segment. D_1-like receptors stimulate intracellular cAMP signaling pathway through $G\alpha_s$ G-proteins, whereas D_2-like receptors inhibit DA signaling through $G\alpha_{i/o}$ G-proteins.

High D_3R Binding Affinity to DA

Each DA receptor binds endogenous ligand DA with affinities in the nM range. The D_2-like receptor subtypes bind DA with higher affinities than the D_1-like family with D_3R binding DA with the highest affinity (Missale et al. 1998). Therefore, D_3R has been described as being a major receptor underlying DA transmission in the brain reward system. Given that basal levels of extracellular DA (5–10 nM) and synaptic DA (~50 nM) (He and Shippenberg 2000; Ross 1991), it is expected that a fraction of D_3R is constitutively activated, thus playing an essential role in both tonic and phasic DA signaling.

Restricted D_3R Distribution

The human D_3R was first cloned in 1990 (Giros et al. 1990), which was followed by the cloning and characterization of the rat D_3R (Sokoloff et al. 1990). Since then, various radiolabeled ligands such as [^{3}H]7-OH-DPAT), [^{3}H]PD-128907, and [^{125}I] epidepride were developed (Hall et al. 1996; Herroelen et al. 1994; Murray et al. 1994). A variety of techniques such as quantitative autoradiography and in situ mRNA hybridization have been used to map the distribution of D_3R in the brain and periphery.

Using a polyclonal D_3R antibody, Diaz et al. detected dense D_3R-immunostaining mainly in the islands of Calleja and mammillary bodies, moderate to low signals in the shell of NAc, frontoparietal cortex, SNc, VTA, and lobules 9 and 10 of the cerebellum, but very low or no signal in other rat brain regions such as DST (Diaz et al. 2000; Lammers et al. 2000). However, due to the concerns of DA receptor antibody specificity, autoradiography and PET imaging have become the major techniques to map D_3R distributions in the brain (Diaz et al. 2000; Lammers et al. 2000). Consistent with the findings by immunostaining, an autoradiogram study with [^{125}I]7-OH-PIPAT also showed the restricted distributions of D_3R in the rat brain with the highest level of D_3R expression in the islands of Calleja, ventromedial shell of NAc, VP, and SN (Stanwood et al. 2000). Such a restricted distribution of D_3R expression was also found in other species, such as mouse, guinea pig, and rabbit (Diaz et al. 1994, 1995; Levant 1998). Among these four species the mouse shows high density D_3R expression in hippocampus and low expression in the frontal cortex (Levant 1998).

Subsequent PET imaging studies showed that [^{11}C](+)-PHNO, a mixed D_2R/D_3R agonist (Narendran et al. 2006; Seeman et al. 2005) produces preferential uptake in the ventral pallidum and globus pallidus of humans and baboons in contrast to radiolabeled D_2R antagonists (such as [^{11}C]raclopride) or other D_2R agonists (such as [^{11}C]NPA) that show preferential uptake in the dorsal striatum (Gallezot et al. 2012; Ginovart et al. 2007; Graff-Guerrero et al. 2008; Kiss et al. 2011; Narendran et al. 2009; Rabiner and Laruelle 2010; Rabiner et al. 2009). The specific binding of [^{11}C](+)-PHNO in the globus pallidus of baboons was inhibited by the partial D_3R agonist BP-897 (*N*-[4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl]naphthalene-2-carboxamide) suggesting that the D_3R contribution to the specific binding signal of [^{11}C](+)-PHNO is higher than that of [^{11}C]raclopride (Doot et al. 2019).

The distribution of the D_3R gene in rats and mice is well established. Figure 2 shows the overall brain distribution of D_1, D_2, and D_3 transcripts in mice using in situ hybridization (ISH) assays. D_1R mRNA is highly expressed in the basal ganglia, including the DST, NAc, and olfactory tubercle (Monsma et al. 1990). D_2R mRNA displays similar regional distribution as the one of D_1R mRNA (Gerfen et al. 1990). In addition, D_2R mRNAs were found in dopaminergic cell bodies within the SNc and VTA (Bunzow et al. 1988). In contrast, the highest level of D_3R mRNA was seen in the islands of Calleja, the NAc, hippocampus (Hipp), and insular cortex in rats (Fig. 3) (Bouthenet et al. 1991; Landwehrmeyer et al. 1993a; Sokoloff et al. 1990). The levels of D_4R and D_5R mRNA in the striatum are very low (Meador-Woodruff et al. 1992; O'Malley et al. 1992).

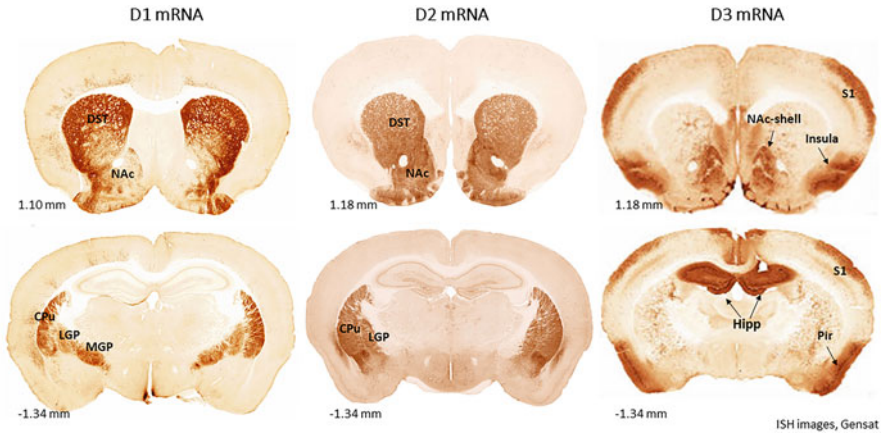

Fig. 2 D_3 mRNA expression in rat brain as assessed by ISH at the level of the NAc (up panels) and thalamus (lower panel). *DST* dorsal striatum, *NAc* nucleus accumbens, *S1* primary sensory cortex, *CPu* caudate putamen, *LGP* lateral globus pallidus, *MGP* medial globus pallidus. From the public (NIH) database at: https://www.ncbi.nlm.nih.gov/probe/docs/projgensat/

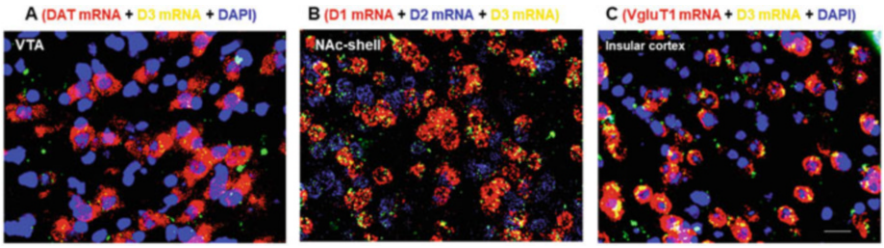

Fig. 3 RNAscope in situ hybridization results, illustrating that low density D_3R mRNA is expressed in a subpopulation of dopaminergic neurons in the VTA (**a**, red—DAT-positive dopamine neurons; yellow—D3 mRNA signal; blue—DAPI-labeled nuclei), while high density D_3R mRNA is expressed in NAc D_1-MSNs (red) (**b**, red—D1-MSNs; yellow—D3 mRNA signal; blue—DAPI-labeled nuclei) and insular glutamate neurons (red) in mice (**c**, red—VgluT1-positive glutamate neurons; yellow—D3 mRNA signal; blue—DAPI-labeled nuclei) (Xi ZX et al., unpublished data)

In the *post-mortem* human brain, D_3R mRNA expression was found on principal cells of the prefrontal cortex (PFC) and abundant in basal ganglia, but low level of expression was also evident in cingulate cortex and subcortical regions (including thalamus, Amy, locus coeruleus, raphe nuclei, etc.) (Gurevich and Joyce 1999; Landwehrmeyer et al. 1993b; Larson and Ariano 1995; Suzuki et al. 1998). In contrast to the rat, in human no D_3R mRNA was detected in the VTA (Gurevich and Joyce 1999). Combination of [^{11}C]-(+)-PHNO PET imaging results with brain D_3R and D_2R mRNA expression demonstrated highest level of [^{11}C]-(+)-PHNO binding in the VP, globus pallidus, NAc. There is strong correlation between [^{11}C]-(+)-PHNO binding and D_3R mRNA, but not D_2R mRNA, expression (Komorowski et al. 2020). In addition, using [^{3}H]-PD128907, high densities of D_3R binding were

also observed in the superficial layers of the dorsal horn at cervical and lumbar levels followed by the pars centralis and dorsal horn (Levant and McCarson 2001).

Cellular Distribution of D_3R

To understand which neural substrates underlie D_3R function, it is critical to understand which types of cells express D_3R. Using a polyclonal D_3R antibody, Diaz et al. detected D_3R-immunostaining in all tyrosine hydroxylase (TH)-positive DA neurons in the VTA, SNc, and A8 retrorubral fields, suggesting that D_3R may act as a functional autoreceptor regulating DA neuron activity and DA release from their projection terminals (Diaz et al. 2000). Using double-staining ISH methods to examine D_3 mRNA expression in the NAc (Le Moine and Bloch 1996), the D_3R mRNA is detected in a subpopulation of D_1- or D_2-expressing medium-spiny neurons (MSN)s, and also, in substance P- or enkephalin-expressing neurons, implying that DA may act on each population of postsynaptic neurons in the NAc, producing DA-dependent effects. Given that commercially available DA receptor antibodies (including anti-D_3 antibodies) display poor receptor specificity (Bodei et al. 2009) and classical ISH images display poor mRNA signal resolution at cellular levels, the above findings regarding the D_3R cellular distribution could not be conclusive. Recently, using more specific and sensitive fluorescent D_3R reporter mice, Clarkson and colleagues identified D_3R signal in a small population of pyramidal neurons in the layer 5 of the PFC (Clarkson et al. 2017). We have recently used a highly sensitive and specific RNAscope ISH assays to detect the cellular distribution of D_3R mRNA. We found that D_3R mRNA is expressed only in a subpopulation of dopamine neurons in the VTA, while high density D_3R mRNA is detected in dopamine D_1R-expressing medium-spiny neurons (D_1-MSNs) in the NAc-shell and vesicular glutamate transporter 1 (VgluT1)-positive glutamate neurons in the insular cortex of mice (Fig. 3), indicating that such new advanced techniques are highly valuable in identifying the cellular distributions of D_3R genes or protein in different brain regions and tissues.

2.2 Relationship to Neural Targets and Therapeutic Potential

The exact loci and neural substrates that D_3R antagonists/partial agonists target in the brain are not fully understood. Based on the restricted regional and cellular distributions of D_3R described above, it is reasonable to predict that both presynaptic and postsynaptic D_3R mechanisms may underlie the therapeutic effects of D_3R antagonists/partial agonists in animal models of drug addiction (Fig. 4).

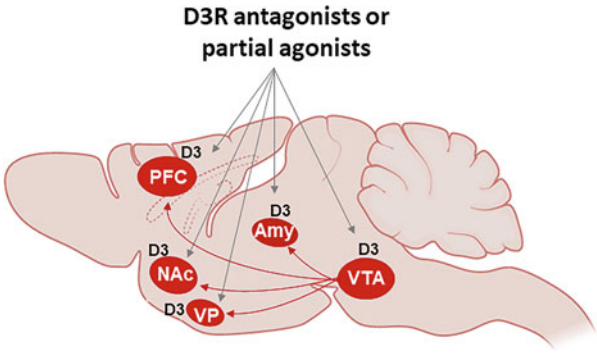

Fig. 4 Schematic diagram of the mesolimbic DA projection system in rat brain, illustrating where high densities of D_3R binding or mRNA are found or upregulated by chronic use of psychostimulants or opioids, which may constitute important targets that D_3R antagonists or partial agonists act

2.2.1 Presynaptic D_3R Mechanism

As stated above, both systemic administration of psychostimulants and opioids produce an initial increase in extracellular DA in the NAc and DST, whereas prolonged withdrawal or abstinence seems to trigger a "hypodopaminergic state" in the mesolimbic DA system, which is closely associated with craving and relapse to drug seeking (Blum et al. 2021a, b; Luscher and Pascoli 2021; Salin et al. 2021; Samaha et al. 2021; Sanna et al. 2021). One may therefore hypothesize that normalization of decreased DA transmission in the reward circuits may decrease drug craving and relapse to drug-seeking behavior. Growing evidence indicates that activation of D_3R by the agonist PD-128907 inhibits DA release in the NAc and PFC possibly via presynaptic D_3 autoreceptors on DA terminals (Millan et al. 2010), while D_3R antagonists/partial agonists produce an increase in extracellular DA levels in the NAc, PFC, or ventral hippocampus possibly by presynaptic D_3 autoreceptor disinhibition (Gobert et al. 1996; Huang et al. 2019; Lacroix et al. 2003; Millan et al. 2000). Thus, we propose that blockade of presynaptic D_3R may in part normalize (restore) the hypodopaminergic state, and therefore, contribute to the therapeutic effects of D_3R antagonists in preventing relapse to drug seeking after abstinence.

In addition, previous studies have shown that D_1R or D_2R agonism improves various aspects of cognitive performance in rodents as well as primates (Cai and Arnsten 1997; Marino and Levy 2019; Nakako et al. 2013). Accordingly, elevated extracellular DA after D_3R antagonism may in turn stimulate D_1R and D_2R in both the NAc and PFC (Clarkson et al. 2017), producing pro-cognitive and pro-social behavioral changes. Thus, indirect D_1R or D_2R activation following presynaptic D_3R antagonism may also in part contribute to D_3R antagonists' effects on cognition and motivation for drug-seeking behavior.

2.2.2 Postsynaptic D_3R Mechanisms

In addition to the presynaptic D_3R mechanism, blockade of postsynaptic D_3R in the brain reward circuits may also underlie D_3R antagonists' action in reducing drug-taking and drug-seeking behavior.

NAc D_3R Mechanism

Recent optogenetic studies indicate that activation of D_1-MSNs in the NAc is associated with positive reinforcement, while activation of D_2-MSNs is mostly associated with aversion (Kravitz et al. 2012; Lobo et al. 2010). Accordingly, it was hypothesized that the acute rewarding effects of psychostimulants or opioids are most likely mediated by activation of D_1-MSNs via Gs-coupled D_1R and inhibition of D_2-MSNs via Gi-coupled D_2R (Hikida et al. 2013; Kravitz et al. 2012; Smith et al. 2013; Yawata et al. 2012). As stated above (Fig. 3), D_3R appears to be co-expressed mainly in D_1-MSNs and less in D_2-MSNs in the NAc-shell. Thus, we hypothesize that blockade of D_3R in D_1-MSNs would cause D_1-MSN disinhibition and increase their excitability, which may normalize the hypodopaminergic state observed in chronic drug users, and therefore, decrease craving and motivation for drug-seeking behavior. In contrast, blockade of D_3R in D_2-MSNs would also disinhibit D_2-MSNs and increase their excitability, and therefore, potentiate D_2-MSN-mediated aversive effects. However, D_3R expression in D_2-MSNs is very low (Fig. 3), and therefore, D_3R antagonist action in D_2-MSNs should be minimal. Thus, the final net effect of D_3R antagonism on brain reward function would be mediated mainly by blockade of D_3R on postsynaptic D_1-MSNs. Furthermore, blockade of D_3R directly counteracts DA action after acute drug administration.

VP D_3R Mechanism

The VP is a key hub within the reward system that mediates drug-taking and drug-seeking behaviors (Creed et al. 2016; Heinsbroek et al. 2020). Previous studies have shown that drugs of abuse enhance DA release within the VP and produce reinforcing effects (Panagis and Spyraki 1996). As stated above, high density D_3R is expressed in the VP. Thus, blockade of VP D_3R may also in part explain how D_3R antagonists attenuate the rewarding effects produced by psychostimulants or opioids under certain experimental conditions. In addition, Pribiag et al. (2021) recently reported that 2 weeks of forced abstinence from cocaine self-administration upregulates D_3R expression in VP GABAergic neurons, which project to the lateral habenula (LHb). Activation of D_3R in VP GABAergic neurons underlie contextual cue-induced cocaine-seeking behavior in rats via a VP-LHb circuit (Campbell and Lobo 2021; Pribiag et al. 2021). In the LHb, glutamatergic neurons project to the RMTg, where GABAergic neurons project to DA neurons in the VTA and

functionally modulate DA neuron activity (Jhou et al. 2009). These findings suggest that D_3R in VP GABA neurons may regulate VTA DA neuron activity via a VP-LHb-RMTg-VTA circuit, and therefore, modulate cocaine-seeking behavior. Accordingly, blockade of VP D_3R may also explain how D_3R antagonists attenuate drug- or cue-induced drug-seeking behavior.

PFC D_3R Mechanism

An early study indicated low levels of D_3R are expressed in the PFC (Larson and Ariano 1995), suggesting possible involvement of cortical D_3R in the cognitive effects of D_3R ligands (Nakajima et al. 2013). This is supported by a recent finding that a unique population of PFC principal neuron in layer 5 expresses D_3R (Clarkson et al. 2017). Notably, such D_3R-expressing cortical neurons lack expression of D_1 or D_2 receptor and activation of D_3R in PFC neurons inhibits low-voltage-activated $Ca_V3.2$ calcium channels at the axon initial segment, causing a reduction in action potential (AP) firing. Importantly, the D_3R-expressing PFC neurons send axonal projections to the contralateral cortex, NAc, and basolateral amygdala (BLA), thereby possibly modulating drug-taking and drug-seeking behavior via PFC-NAc and PFC-BLA circuits (Clarkson et al. 2017).

Insula D_3R Mechanism

The insula is another node involved in the networks underlying SUD (Naqvi and Bechara 2009). The general notion emerging from recent studies is that drug craving and cue-induced urges could be complex interoceptive emotions that are processed in the insular cortex, particularly in its anterior part. Several studies in humans and experimental animals indicated insula lesions diminished drug-seeking behaviors (Contreras et al. 2007; Naqvi et al. 2007), an effect that was even more pronounced by combined damage of the insula and putamen (Gaznick et al. 2014), suggesting an abnormal connectivity of these two regions in SUD. This is further supported by a recent finding that alcoholism is associated with a loss of insula gray matter (Senatorov et al. 2015), and decreased functional connectivity between the NAc and insula was observed in alcohol-dependent rats (Scuppa et al. 2020) and aversion-resistant alcohol intake in rodents (Seif et al. 2013; Sullivan et al. 2013). The mechanisms and significance of this action remain unclear. Given that a hypodopaminergic state within the brain reward circuitry is a hallmark of an addicted state and that D_3R mRNA is detected in presynaptic DA neurons in the VTA and postsynaptic glutamate neurons in the insular cortex (Fig. 3C), we predict that presynaptic D_3R antagonism in the insula may also contribute to the normalization of the hypodopaminergic status, and therefore, improve the insula-NAc functional connectivity. Similarly, blockade of postsynaptic D_3R in the insula would also counteract the action produced by elevated DA after acute cocaine or opioid administration.

Amygdala (Amy) D_3R Mechanism

In addition to the above brain regions, the Amy is also involved in drug-taking and drug-seeking behavior. The Amy receives dopaminergic innervation (Asan 1997) and has high D_3R expression (Herroelen et al. 1994; Murray et al. 1994; Suzuki et al. 1998; Tupala et al. 2001). Cocaine injections or exposure to cocaine-associated cues activates the Amy in animals and humans as assessed by neuroimaging and c-fos expression studies (Grant et al. 1996; Neisewander et al. 2000) and increase D_3R expression in the Amy (Guerrero-Bautista et al. 2021). Amy lesions or microinjections of D_3R receptor antagonists inhibit cocaine self-administration and contextual cue-induced cocaine seeking (McGregor and Roberts 1993; Xi et al. 2013). Microinjections of psychostimulants into the central amygdala (CeA), but not the BLA, produce a conditioned place preference, whereas selective lesions of the BLA do not affect cocaine self-administration (Meil and See 1997; Yun and Fields 2003), suggesting dissociable roles for the CeA and BLA in cocaine-related behavior (Li et al. 2008; Lu et al. 2005; O'Dell et al. 1999). The D_3R expression and function in the CeA vs. BLA in psychostimulants or opioid action remain to be determined.

2.3 D_3R Neuroadaptations Due to SUD

A growing body of evidence suggests that aberrant D_3R signaling contributes to several brain disorders. Consequently, D_3R has emerged as a potential therapeutic target in the treatment of major neurological and neuropsychiatric disorders such as schizophrenia, Parkinson's disease, and SUD. However, the mechanisms underlying D_3R signaling are poorly understood, either in healthy or diseased brain. Therefore, unraveling the unknown downstream signaling pathways activated by D_3R in both the healthy and the diseased brain is likely to reveal new therapeutic strategies toward DA-associated disorders.

2.3.1 Development Changes in D_3R Expression

Brain D_3R mRNA is detected early in development and continually expressed during the postnatal period (Araki et al. 2007; Gurevich et al. 1999; Levant 1997). ISH assays indicate that D_3R mRNA expression is restricted, almost entirely to the ventricular neuroepithelium during the whole prenatal ontogeny and that the neuronal expression of the D_3R appears during the first postnatal week (after the DA innervation) (Diaz et al. 1997; Stanwood et al. 1997), suggesting that the increase in D_3R mRNA expression in adults is likely to reflect functional changes in the dopaminergic innervation of the ventral striatum (Shafer and Levant 1998). This is supported by the findings that a lesion of DA neurons, impairment of axonal transport, or reduction of DA neuron firing causes a reduction in D_3R gene expression (Levesque et al. 1995) and repeated treatment with levodopa rescued D_3R

mRNA expression in the NAc and induced an ectopic expression within the dorsal striatum (Bordet et al. 1997).

2.3.2 Tolerance and Desensitization after D_3R Activation

DA induces only a marginal fraction of D_3R to translocate from cell surface to intracellular vesicles, in stark contrast to D_2R (Kim et al. 2001; Min et al. 2013), suggesting that D_3R undergoes limited agonist-induced internalization. However, recent studies indicate that D_3R agonists are able to induce D_3R desensitization and internalization (Xu et al. 2019) via multiple intracellular signal mechanisms, including protein kinase C (PKC)- and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII). Desensitization may occur at homodimeric and heterodimeric D_3R. For example, D_1R-D_3R heterodimers can be internalized in response to the paired stimulation of both D_1R and D_3R via a β-arrestin-dependent mechanism in human embryonic kidney 293 cells (Fiorentini et al. 2008; Westrich et al. 2010). PKC-mediated phosphorylation of D_3R can also induce clathrin-mediated D_3R endocytosis and lysosomal D_3R degradation (Zhang et al. 2016b). CaMKII-mediated D_3R desensitization is intracellular Ca^{++}-dependent, and therefore, is associated with neuronal activity (Liu et al. 2009). Palmitoylation is another post-translational modification that can regulate D_3R activity. Palmitoylation is essential for cell surface expression, PKC-mediated endocytosis, and agonist-induced tolerance of D_3R (Zhang et al. 2016a). Compared with D_2R, D_3R undergoes a more extensive palmitoylation on its cysteine residues at the carboxyl terminus tail.

2.3.3 Neuroadaptations after Exposure to Drugs of Abuse

In vitro and in vivo studies in experimental animals suggest that drugs of abuse may cause D_3R signaling abnormalities. In vitro, cocaine increases dendritic arborization and soma area in cultured dopaminergic neurons from mouse via D_3R-dependent activation of ERK and Akt (Collo et al. 2012). In rats, nicotine upregulates D_3R, but reduces D_3nf mRNA levels in the NAc, and therefore, increasing the D_3R/D_3nf ratio (Smith et al. 2015). In humans, chronic drug use induces long-lasting neuroadaptations in D_3R expression, although some of the findings are conflicting (Richtand 2006). PET imaging studies with the D_3R-preferring radioligand [^{11}C](+)PHNO have shown higher number of available D_3R in the SN, hypothalamus, and Amy of patients who are addicted to cocaine, compared with healthy controls (Matuskey et al. 2014). Notably, SN D_3R levels correlated with years of cocaine use. Consistent with this finding, a six-fold increase in D_3R mRNA levels was found in the NAc of cocaine overdose victims, as compared with age-matched and drug-free control subjects (Segal et al. 1997). Similarly, increased [^{11}C](+)PHNO binding is also observed in the SN of methamphetamine users (Boileau et al. 2016), and in the hypothalamus of alcohol-dependent patients (Erritzoe et al. 2014). Furthermore,

the functionally enhanced D_3R-Gly-9 variant was associated with the development of early-onset heroin dependence in a Chinese population (Kuo et al. 2014).

The neural mechanisms underlying D_3R upregulation after chronic drug abuse are unclear. As stated above, almost all drugs of abuse increase extracellular DA and subjects with chronic drug use display hypodopaminergic states in the mesolimbic system (Leyton and Vezina 2014; Luscher and Pascoli 2021; Ron and Jurd 2005; Samaha et al. 2021). These findings suggest that the changes in D_3R signaling (desensitization vs. upregulation) could be adaptative or compensatory responses to changes in extracellular DA. This is supported by the finding that DA depletion induces compensatory increases in the number and the affinity of D_3R to endogenous DA or exogenous DA receptor ligands (Avalos-Fuentes et al. 2015; Prieto et al. 2011). A better understanding of how drugs of abuse alter D_3R activity may uncover pathophysiologic mechanisms underlying SUD and lead to discovery of novel molecular targets for pharmacotherapeutic treatment.

2.4 Relationship of D_3R to Pain

Previous studies have explored the role of DA receptors in opioid analgesia and tolerance. The majority focused on the D_2R and showed that nonspecific D_2-like receptor ligands (agonists or antagonists) are able to prevent morphine tolerance (Dai et al. 2016; Gomaa et al. 1989; Ozdemir et al. 2013). To dissect the role of different D_2-like receptor subtypes in this action, the D_3-preferring agonists 7-OH-DPAT and pramipexole were also tested. It was found that both the compounds can prevent tolerance to opioids (Cook et al. 2000; Rodgers et al. 2020; Zarrindast et al. 2002), suggesting that D_3R mechanisms may be also involved in opioid analgesia. This is supported by our recent finding that both the highly selective D_3R antagonists/partial agonists (VK4-116 and VK4-40) attenuate oxycodone self-administration and reinstatement to drug seeking, but without compromising oxycodone's antinociceptive effects in rats (Jordan et al. 2019b; You et al. 2019). In fact, a potentiation effect on oxycodone analgesia was observed at higher doses.

However, the neural mechanisms underlying this D_3R modulation of opioid analgesia are poorly understood. Early studies indicate that intra-NAc or VTA microinjections of a DA receptor antagonist blocks noxious stimuli-induced antinociception (Altier and Stewart 1998; Gear et al. 1999), suggesting that the mesolimbic DA system could be one of the major loci that D_3R antagonists modulate pain and opioid analgesia (Schmidt et al. 2002). In addition, the spinal cord could be another important location underlying DA and opioid interactions as DA (D_1, D_3) and MOR receptors are detected in the dorsal horn (Abbadie et al. 2001; Levant and McCarson 2001). This is further supported by the finding that genetic deletion of D_3R in D_3-mutant mice altered pain-associated responses and morphine-induced antinociception at the spinal cord (Brewer et al. 2014; Clemens and Hochman 2004; Keeler et al. 2012). Furthermore, considerable evidence suggests an interaction between the D_1R and D_3R or between D_3R and MOR receptors. The D_3R has

been shown to colocalize with D_1R or form D_1-D_3 heterodimers in the striatum (Fiorentini et al. 2008, 2010), which has been reported to modulate opioid analgesia and reward (Rodgers et al. 2019). In addition, D_3R and MOR are colocalized with D_1R in NAc D_1-MSNs (Galaj et al. 2020a), suggesting the possible presence of functional D_3-MOR heterodimers. Given that both D_3R and MOR modulate intracellular adenylate cyclase and cAMP levels, it is suggested that the D_3R and MOR interaction may occur at intracellular cAMP/PKA level (Zarrindast et al. 2002; Zhang et al. 2008, 2012).

2.5 Relationship to Other Comorbid Neuropsychiatric Disorders

There is significant comorbidity between neuropsychiatric and SUD, which may be particularly evident in women (Chander and McCaul 2003). Persons living with affective and anxiety disorders are more likely to use alcohol or drugs of abuse. Recognition for both psychiatric and SUD comorbidity is important for improving treatment outcomes for these co-occurring conditions.

SUD and major depressive disorder (MDD) are prevalent and frequently co-occur (Volkow 2004). Comorbidity between bipolar disorder (BPD) and SUD is also highly prevalent (Post and Kalivas 2013; Salloum and Brown 2017). Lifetime prevalence estimates of depression are 30 ~ 50% among persons with cocaine use disorder (CUD) (Conway et al. 2006). The presence of depressive symptoms is associated with poorer outcomes in CUD (Leventhal et al. 2006; Raby et al. 2014). Anhedonia is a core symptom of MDD and characterized by reduced experiencing of pleasure. Anhedonia has been linked to DA dysfunction in the mesolimbic system (Der-Avakian and Markou 2012). In rodents, lower DA concentrations in the NAc have been associated with fewer attempts to work for rewards (Manduca et al. 2016). In humans, decreased DA response to psychostimulants, decreased availability of striatal $D_{2/3}$ receptors, and increased availability of DA transporters have been observed and associated with a "reward deficiency" state in patients with MDD (Koob 2013). This hypodopaminergic state may in part explain such negative symptoms experienced during abstinence as dysphoria, anhedonia, and craving, which may lead to higher reward pursuits and motivation for using illicit drugs or precipitating relapse. Accordingly, prescription stimulants such as dextroamphetamine have been proposed to address such reward deficiency in a way similar as methadone for OUD (Angarita et al. 2021b) and antidepressants have been used for the treatment depression and SUD comorbidity (Zhou et al. 2015). However, a major concern with stimulants, such as amphetamine, is their abuse potential. An alternative strategy to minimize this potential risk involves the development and use of atypical DAT inhibitors (Newman et al. 2021). In addition, the D_3R antagonists/partial agonist could be promising for the treatment of the CUD and MDD comorbidity (Keck et al. 2015; Newman et al. 2012) since blocking presynaptic D_3R may

facilitate DA release and normalize the hypodopaminergic status, while activation of postsynaptic DA receptors by DA or D_3R partial agonists may not only mitigate withdrawal effects during abstinence but also improve dysphoria and anhedonia in patients with SUD and MDD comorbidity.

Anxiety disorders (AD) are characterized by excessive fear, anxiety, and related behavioral disturbances (Craske et al. 2017). Epidemiological studies revealed striking rates of co-occurring anxiety and SUD (Compton et al. 2007; Rogers et al. 2021). It is well documented that Amy directly modulates anxiety (Kalin et al. 2004; Lesscher et al. 2008). Early research emphasized a role of DA in the pathophysiology of anxiety (Taylor et al. 1982), which recently has been reinvigorated (Dedic et al. 2018; Kienast et al. 2008) as the Amy provides the main input to midbrain DA neurons (Fudge and Haber 2000). A recent study investigated the relationships between AD and brain $D_{2/3}$ functional activity and functional connectivity. It was found that higher DA release in the Amy was associated with lower trait anxiety and lower cingulate–amygdala functional connectivity, suggesting that a negative relationship between DA functional activity and anxiety levels and a hypodopaminergic state may also exist in AD (Berry et al. 2019). Accordingly, we hypothesize here that D_3R antagonists/partial agonists may also be useful for the treatment of SUD and AD comorbidity since blockade of presynaptic D_3R may increase DA release and activation of postsynaptic D_3R by DA or partial D_3R agonist may normalize decreased DA transmission, thereby producing anxiolytic effects.

3 D_3R Antagonists and Partial Agonists Currently under Preclinical Investigation for SUD

3.1 Past D_3R Preferential and Selective Antagonists that Were Tested in Clinical Trials

To the best of our knowledge, there have been only a few selective D_3R antagonists (GSK598809) or preferential D_3R partial agonists (buspirone, cariprazine) that have been available clinically and only buspirone has been directly tested in a clinical study for CUD (Bergman et al. 2013).

3.1.1 GSK598809

GSK598809 (Fig. 5) is a selective D_3R antagonist with ~120-fold selectivity for D_3R ($K_i = 6.2$ nM) over D_2R ($K_i = 740$ nM) (Micheli et al. 2010; Searle et al. 2010). In a clinical study focusing on craving in smokers, a single dose of GSK598809 produced 72% to 89% D_3R occupancy and transiently alleviated craving for cigarette smoking after overnight abstinence (Mugnaini et al. 2013). In addition, GSK598809 effectively reduced appetitive responses to food cues in overweight and obese

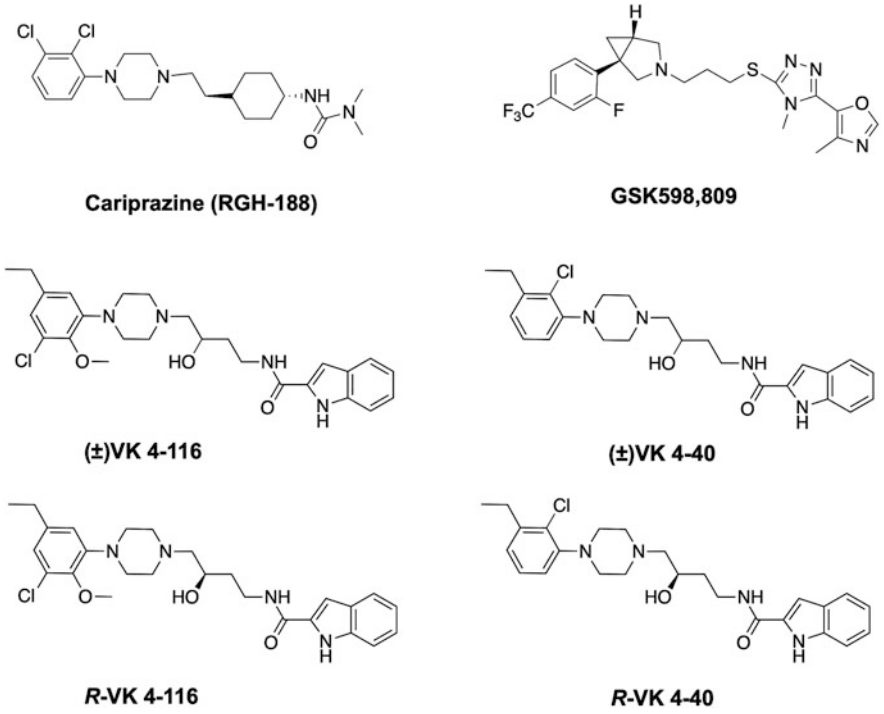

Fig. 5 Chemical structures of lead D_3R antagonists/partial agonists

individuals (Mogg et al. 2012; Nathan et al. 2012). In nonclinical studies in dogs and rats, GSK598809 was reported to increase blood pressure especially in the presence of cocaine (Appel et al. 2015), which dampened enthusiasm for conducting a clinical trial in patients with CUD.

3.1.2 Buspirone

Buspirone is an FDA-approved medication for the treatment of anxiety. Its therapeutic effects are believed to be mediated mainly by its partial agonist action at 5-HT_{1A} receptors $K_{i\text{-High}}$ (19.2 nM) and $K_{i\text{-Low}}$ (111 nM) (Noël et al. 2014). However, buspirone also binds to D_3R ($K_i = 98$ nM) (Bergman et al. 2013; Kula et al. 1994) and it was therefore proposed but failed to be effective for a clinical population with CUD (Bergman et al. 2013; Newman et al. 2012). Paradoxically, clinical studies indicate that buspirone is effective for the treatment of anxiety in individuals with alcohol use disorder (Malec et al. 1996) but not in those with OUD (McRae et al. 2004). Buspirone is also ineffective in prevention of relapse for cigarette smoking (Schneider et al. 1996) or in reductions of drug (cocaine, cannabis) and alcohol consumption (Malec et al. 1996; McRae-Clark et al. 2015;

Winhusen et al. 2014). The mechanisms underlying these negative findings are unclear; however, this may be related to its non-selectivity and low occupancy at the D_3R in human brain (Le Foll et al. 2016) at doses used clinically. So far, there has been no clinical trial to evaluate the effectiveness of buspirone in controlling opioid intake and relapse. However, buspirone has been shown to reduce withdrawal symptoms in heroin addicted individuals (Buydens-Branchey et al. 2005; Rose et al. 2003).

3.1.3 Cariprazine

Cariprazine (Fig. 5; RGH-188) is a D_3R-preferring partial agonist (Citrome 2013; Gyertyan et al. 2007; Kiss et al. 2010), showing approximately ten-fold higher affinity for human D_3R ($pK_i = 10.07$; $K_i = 0.085$ nM) over human D_{2L} ($pK_i = 9.16$; $K_i = 0.49$ nM) and D_{2S} receptors ($pK_i = 9.31$; $K_i = 0.69$ nM). In addition, it is an antagonist with high affinity at human 5-HT_{2B} receptors ($pK_i = 9.24$; $K_i = 0.58$ nM). Cariprazine has been recently approved for the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder, by the FDA. Preclinical studies indicate that cariprazine is able to reduce the rewarding effect of cocaine and relapse to cocaine-seeking behavior with half maximal effective dose (ED_{50} values of 0.2 mg/kg) (Gyertyan et al. 2007; Roman et al. 2013). In addition, a recent case report indicates that cariprazine is able to improve both psychotic and addictive symptoms in subjects with persistent methamphetamine use (Ricci et al. 2022). Notably, a patient reported an abrupt decrease in substance craving and use and an improvement in positive and negative psychotic symptoms. These findings suggest that cariprazine deserves further research as an antipsychotic candidate for the treatment of SUD with bipolar disorder. Indeed, a new clinical trial has recently begun to assess the effectiveness of cariprazine for treatment of comorbid CUD and OUD (Kampman 2021).

3.2 New and Promising D_3R Selective Antagonists/Partial Agonists for SUD

Although developing highly selective D_3R antagonists/partial agonists with improved bioavailability and pharmacokinetics profiles is challenging (Heidbreder and Newman 2010; Keck et al. 2015; Leggio et al. 2016; Pich and Collo 2015), significant progress in medicinal chemistry has been made. High D_3R selectivity maybe essential to minimize D_2R-mediated extrapyramidal and motor side effects that would undoubtedly reduce compliance. Improved bioavailability and pharmacokinetics (PK) profiles are also critical to future translational studies toward the development of novel treatment modalities. Several D_3R antagonists/partial agonists have been developed and tested in experimental animal models and have been

recently reviewed systematically elsewhere (Galaj et al. 2020b; Keck et al. 2015; Newman et al. 2021). Although there are several groups who are continuing to pursue this class of agents toward application to SUD (Ewing et al. 2021; Lv et al. 2019; Thomsen et al. 2017), herein we highlight just a few promising D_3R antagonists/partial agonists for the treatment of OUD and possibly PSUD based on their favorable receptor binding and PK profiles and their pharmacological efficacy in reducing drug-taking and drug-seeking behavior (Fig. 5).

3.2.1 (±)-VK4-116 and its R-Enantiomer

Racemic (±)-VK4-116 is a highly selective D_3R antagonist with ~1700-fold binding selectivity for D_3R ($K_i = 6.84$ nM) over D_2R ($K_i = 11{,}400$ nM) and is also highly selective across >70 receptors, enzymes, and transporters (Kumar et al. 2016, NIDA Treatment Discovery Program). It also showed very high metabolic stability and half-life ($t_{1/2} = 250$, 116 and 102 min in rat, human, and monkey liver microsomes, respectively) (Kumar et al. 2016). (±)-VK4-116 displayed excellent brain penetration, after oral administration (You et al. 2019) and thus was identified as a lead compound with translational potential.

Preclinical studies in rodents with (±)-VK4-116 showed promising results. For example, pretreatment with (±)-VK4-116 dose-dependently reduced the acquisition of oxycodone-induced CPP, oxycodone self-administration under FR2 and PR reinforcement schedules in rats (You et al. 2019). In addition, pretreatment with (±)-VK4-116 decreased the escalation of oxycodone self-administration in male and female rats with extended access to drug (de Guglielmo et al. 2019), facilitated extinction of drug seeking, and reduced oxycodone-primed reinstatement of drug seeking in rats (You et al. 2019). It also reduced oxycodone-induced hyperactivity and repeated oxycodone-induced locomotor sensitization in mice (Kumar et al. 2016). Furthermore, pretreatment with (±)VK4-116 dose-dependently reduced naloxone-precipitated conditioned place aversion in rats (You et al. 2019) and withdrawal-induced hyperalgesia and irritability-like behaviors (de Guglielmo et al. 2019), suggesting that (±)-VK4-116 has the ability to attenuate opioid withdrawal symptoms, a critical aspect for therapeutic utility (Koob 2021). Notably, (±)-VK4-116 has been shown to potentiate the analgesic effects of oxycodone, as assessed in a hot plate assay (You et al. 2019). This unique characteristic of (±)-VK4-116 not only supports its potential utility in the treatment of opioid use disorders (OUD) but also suggests its coadministration with prescription opioids in pain management as lower doses of prescription opioids could be used to mitigate pain when combined with (±)-VK4-116, and thus reduce the risk of abuse and the development of dependence. Of note, *R*-VK4-116 (Fig. 5) is also a highly D_3R-selective antagonist (Shaik et al. 2019) and is currently under development for treatment of OUD.

3.2.2 (±)-VK4-40 and its Enantiomers

Racemic (±)-VK4-40 (Fig. 5) is another newly developed and low efficacy D_3R partial agonist with high affinity for D_3R ($K_i = 0.36$ nM) over D_2R ($K_i = 151$ nM) and ~ 400-fold selectivity (Kumar et al. 2016). The *R*-enantiomer (*R*-VK4-40) is a D_3R antagonist, whereas the *S*-enantiomer is a partial agonist, like the racemate. *R*-VK4–40 displays high affinity for D_3R ($K_i = 0.29$ nM) over D_2R ($K_i = 75.8$ nM) and 261-fold selectivity for D_3R over D_2R (Shaik et al. 2019). The *S*-enantiomer is equally D_3R-selective. (±)-VK4–40 was shown not only to attenuate cocaine-primed reinstatement and cocaine-enhanced brain-stimulation reward maintained by optical stimulation of VTA DA neurons, but also to reduce cocaine self-administration across multiple cocaine doses under an FR2 schedule (Jordan et al. 2020), suggesting that (±)-VK4-40 is a potential D_3R partial agonist candidate for the treatment for PSUD.

R-VK4–40 is metabolically stable in the presence of NADPH with 86% remaining level in the plasma over 1 h and showed excellent brain penetration after oral administration in rats (Jordan et al. 2019b). In animal models of OUD, *R*-VK4-40 dose-dependently inhibited oxycodone self-administration maintained under FR1 and PR schedules of reinforcement in rats and attenuated oxycodone-enhanced ICSS maintained by optical activation of VTA DA neurons in mice (Jordan et al. 2019b), suggesting that *R*-VK4-40 can reduce the rewarding effects of opioids. Notably, *S*-VK4-40 displayed similar pharmacological efficacy, as *R*-VK4-40, in attenuation of cocaine-enhanced brain-stimulation reward in the optical intracranial self-stimulation (ICSS) assays (Galaj et al. 2020b; Newman et al. 2021). Pretreatment with *R*-VK4–40 did not compromise the analgesic effects of oxycodone and in fact, it increased latencies to emission of thermal nociceptive response, shifting the oxycodone-dose response curve upward (Jordan et al. 2019b), suggesting an additive analgesic effect to oxycodone. *R*-VK4-40 alone also produced analgesic effects without affecting locomotor activity or performance on the rotarod test (Jordan et al. 2019b). The neural mechanisms underlying *R*-VK4-40-induced analgesic effects are yet to be determined. A possible interaction between D_3R and MOR may occur in the dorsal horn of the spinal cord (Abbadie et al. 2002; Levant and McCarson 2001; Ray and Wadhwa 2004), which may in part underlie the potentiation of opioid analgesia after D_3R antagonism (Jordan et al. 2019b).

3.2.3 Dual-Target Mu Opioid Receptor (MOR): D_3R Partial Agonists

The recognition of D_3R antagonism/partial agonism as an alternative and nonopioid approach for treatment of OUD without compromising opioid analgesia, combined with the possible presence of D_3R-MOR heterodimers prompted us to develop a novel class of dual-target ligands with MOR partial agonist and D_3R antagonist/partial agonist profiles (Bonifazi et al. 2021). The idea was that these molecules would, on the one hand, block D_3R, mitigating the reinforcing effects of opioids as

reported previously (de Guglielmo et al. 2019; Jordan et al. 2019a; Kumar et al. 2016; You et al. 2017, 2019), while, on the other hand, partially activate MORs, producing additive or synergistic effects on opioid analgesia as D_3R antagonism potentiates opioid analgesia. This drug design may lead to the development of safer dual target drugs, bridging the most promising pharmacological effects of two classes of molecules/targets previously developed independently.

3.3 Potential Challenges: Cardiovascular Toxicity in the Presence of Cocaine

Although D_3R has long been a focus of medication development for addiction, translational potential of D_3R-targeted ligands to clinical settings has, to date, been limited. One potential safety concern relates to cardiovascular effects after systemic administration. This is based on the finding that the D_3R, in addition to their CNS expression, are also found in the kidney, regulating blood pressure. It was reported that blockade of peripheral D_3R may cause sodium retention and possibly hypertension by antagonizing the inhibitory effects of DA on sodium transport (Zeng et al. 2004, 2008). Such effects were observed in mice with genetic deletion of D_3R that developed elevated systolic blood pressure and diastolic hypertension (Jose et al. 1997). In addition, two older D_3R antagonists SB277011A and GSK598809 were reported to produce an increase in blood pressure in dogs and rats, particularly in the presence of cocaine (Appel et al. 2015).

To further address this issue, we have recently examined the cardiovascular effects of the novel D_3R compounds *R*-VK4-116 and *R*-VK4-40 in comparison with SB-277011A and L-741,626 (a selective D_2R antagonist) as controls. In this study, we found that neither *R*-VK4-116 nor *R*-VK4-40 exhibited adverse cardiovascular effects (Jordan et al. 2019b), while both SB277011A and L-741,626 did. In rats implanted with telemetric devices, cocaine or oxycodone produced a small increase in blood pressure, heart rate, body temperature, and locomotor activity, while *R*-VK4-116 produced a reduction in body temperature when administered alone (Jordan et al. 2019b). However, pretreatment with *R*-VK4-116 significantly reduced oxycodone-induced increases in body temperature and blood pressure. Similarly, cocaine-induced increases in blood pressure and heart rate were also attenuated by *R*-VK4-116 (Jordan et al. 2019b). Moreover, *R*-VK4-40 also lacks these adverse cardiovascular effects. *R*-VK4-40 alone reduced blood pressure and heart rate in rats, while pretreatment with *R*-VK4-40 attenuated oxycodone-induced increases in blood pressure and oxycodone or cocaine-induced increases in heart rate and body temperature (Jordan et al. 2019b). Greater selectivity for D_3R over other receptors (e.g., D_1, D_2, or 5-HT receptors) could be an important reason why *R*-VK4-116 and *R*-VK4-40 do not share the cardiovascular effects of other older D_3R antagonists (SB-277011A and GSK598809) since many other receptors also regulate cardiovascular function (Alves et al. 2019; Cuevas et al. 2013; Yang et al. 2021).

Nevertheless, these unique characteristics make both *R*-VK4-116 and *R*-VK4-40 attractive lead candidates in translational medicine for OUD and PSUD.

4 Perspective on Clinical Application as Treatments for SUD

4.1 Limitations and Advances in the Translational Value of Animal Models of SUD

Based upon their favorable preclinical safety profiles and overwhelming evidence of efficacy in animal models of reinstatement to drug-seeking behavior, selective D_3R antagonists would be expected to reduce relapse to drug-, cue-, and stress-driven consumption post-abstinence and to produce some pro-cognitive effects. Before discussing potential clinical applications of selective D_3R antagonists, one must first recognize the inherent limitations of preclinical models, hence limitations in the translational value they carry to clinical research.

To mimic real-world situations, drug delivery should be active (i.e., the subject must have full control over drug delivery), dose-response effects should be systematically observed, and drug exposure should be chronic or sub-chronic rather than acute. Several animal models are based on passive drug administration, systematic dose-response studies are inconsistent, and relatively low exposure to the drug is still observed. Furthermore, evaluations of potential pharmacotherapies for SUD in animal models most often use acute medication pretreatment paradigms. The predictive validity of those models would improve if they were to adopt protocols that include longer periods of medication treatment.

Most reinstatement models include extinction training. Although the latter isolates the influence of the conditioned stimuli on reinstatement from that of the context, response habit or stress, it reduces the face validity of the model given that humans rarely undergo extinction. Thus, models that assess drug seeking after a drug-free abstinence period as opposed to instrumental extinction training may better capture the nature of cue-induced relapse in humans. In the case of abstinence models, the fact that subjects do not undergo extinction training improves the face validity of this model but restricts data interpretation as drug-seeking may actually reflect response habit, novelty-induced stress, exploratory behavior, and/or innate motivation in addition to context-induced incentive motivation for drug.

Despite limitations, recent advances in nonclinical paradigms also show promise in modeling specific DSM-5 criteria for SUD. First, the concept of addiction as a progressive transition from a positive to a negative reinforcement process that drives the motivated behavior somehow reaffirms the importance of withdrawal in addiction. In that respect, measuring the degree of dysphoria produced by drug withdrawal is highly relevant. Second, the escalation in drug intake observed after long-access training and drug intake escalation mimic increased consumption over time. Third,

the increased final ratios observed in progressive ratio paradigms appear to model the increased time and energy expended to obtain the drug. Fourth, the translational value of behavioral economics models to address the notion of discounting of delayed rewards may provide a readout of impulsivity and its related corollary of loss of control. Animal studies investigating the link between abnormal information processing in the mesocorticolimbic system and changes in responding for delayed or intermittent reinforcement are thus extremely valuable. Similarly, procedures examining choice responding under concurrent schedules of reinforcement may provide valuable insight into drug-seeking because the impact of competing reinforcers, and the work required to obtain each, can be measured simultaneously. Finally, significant work remains to be done to explore the mechanisms involved in animal models of craving and relapse and how to relate these mechanisms to vulnerability to SUD.

4.2 Key Translational Medicine Questions Relevant to Clinical Development

The translational value of nonclinical paradigms should be based upon a good understanding of what needs to be achieved for the target patient population and how pharmacodynamic (PD) data can be reliably linked to pharmacological kinetics (PK). This can only be done by answering the following questions: What exactly is the therapeutic indication for the D_3R drug candidate (target product profile)? What is the proposed treatment response profile? What is the proposed clinical route and frequency of dosing? What is the expected efficacious concentration in a physiological fluid (i.e., concentration-effect relationship)? How long should that concentration be maintained to obtain the desired pharmacological response? What, if any, are the biological markers to monitor toxicity and/or therapeutic effects? Do changes in route or delivery rate alter the course of effect? Is response to treatment time-dependent (e.g., onset mechanism, disease progression)? If a valid PK/PD strategy is in place and if a strong PK/PD relationship is characterized, then efficacy and tolerability can be reliably predicted from the PK data and relevant scenarios can be simulated for decision-making or clinical purposes.

The availability of PET ligands as discussed in another chapter significantly strengthens this strategy by providing PK/PD combined with receptor occupancy (RO) estimates. In this case, the investigational D_3R drug can be radiolabeled and its anatomical distribution and binding in the target tissue can be traced. Alternatively, one may assess the extent to which an unlabeled investigational D_3R drug inhibits specific binding of a PET ligand with known receptor affinity. In the latter case, receptor occupancy at the target receptor can be quantified, thereby enabling a deep understanding of the relationship between dose, plasma concentration, occupancy, and pharmacodynamic or clinical effects of the investigational drug. This information, in turn, leads to invaluable information to optimally design clinical Phase 1 and

Phase 2 proof of concept studies. For example, a randomized, double-blind, placebo-controlled, balanced two-way crossover study established a relationship between the occupancy of D_3R in the brain using ex-vivo $^{[125I]}$7OH-PIPAT autoradiography in the rat and [^{11}C](+)-PHNO PET in human, the pharmacokinetic exposure to GSK598809, the ability of GSK598809 to reduce nicotine-seeking behavior using a conditioned place preference paradigm in rats, and the effect of GSK598809 on cigarette craving in smokers (Mugnaini et al. 2013). In this study, a single dose of GSK598809, giving 72–89% levels of D_3R occupancy, transiently alleviated craving in smokers after overnight abstinence. GSK598809 also partially reversed the attentional bias of abstinent smokers as assessed by the Stroop test, a model of selective attention and cognitive flexibility.

The combination of PET and resting-state functional magnetic resonance imaging (fMRI) is another example of translational medicine efforts to support the development of new molecules targeting the D_3R. [^{11}C](+)-PHNO binding combined with fMRI showed that high midbrain D_3R availability is associated with reduced functional connectivity between the orbitofrontal cortex and neuronal networks implicated in cognitive control and salience processing (Cole et al. 2012). Furthermore, using a rat model of chronic intermittent exposure (CIE) to alcohol (i.e., daily cycles of alcohol intoxication and withdrawal over weeks or months to mimic a pattern of alcohol use typically seen in populations with alcohol use disorder), it was shown that a history of alcohol use produced weaker functional connectivity between the insular and the cingulate cortex, but stronger connectivity between the insula and components of the mesolimbic DA system. The selective D_3R antagonist, SB-277011A, however, was shown to normalize the aberrant connectivity induced by CIE to alcohol (Scuppa et al. 2020).

Altogether, these examples emphasize the importance of a thorough PK/PD/RO strategy to determine reliable dosing in humans, and/or to design combined Phase IIb/III trials allowing for more rapid progression of the medication toward regulatory approval. Specifically, they suggest that D_3R are upregulated in persons living with SUD, an effect that is opposite to that found for D_2R. Second, they show that greater dopaminergic transmission at the D_3R may contribute to motivation to use drugs of abuse. Third, they suggest that drug craving and relapse to drug-seeking behavior can be partly explained by disrupted connectivity within highly integrated neuronal networks that are relying on optimal D_3R availability. One may therefore logically suggest that by modulating specific nodes in those networks, selective D_3R antagonists have the potential to "normalize" functional connectivity to significantly reduce reinstatement of drug-seeking and drug-taking behaviors.

4.3 Most Suitable Clinical Paradigms for Medication Development Purpose

Based on the efficacy of selective D_3R antagonists in a wide range of animal models of SUD and preliminary clinical Phase I data, three hypotheses could be tested in the clinic: (1) selective D_3R antagonists enhance the ability to stop using the substance; (2) selective D_3R antagonists have value in treating withdrawal symptoms; (3) selective D_3R antagonists prevent relapse to drug-seeking and drug-taking after abstinence has been achieved (or relapse to heavy use after a reduction in use). Clinical endpoints depend upon which of these efficacy criteria are chosen and can therefore be quit rates, reduction in withdrawal symptoms, or relapse (conversely abstinence) rates over time.

There is no animal model for self-motivated stopping, little is known about the neurochemical substrates of readiness for change (stopping), and there are no data to suggest that selective D_3R antagonists would enhance readiness to stop substance use. There is, however, some evidence to suggest that selective D_3R antagonists would be effective for treating withdrawal symptoms. For example, (±)VK4-116 (You et al. 2018) and SB-277011A were shown to reduce conditioned place aversion (CPA) produced by naloxone-precipitated withdrawal from acute opioid administration (Rice et al. 2012) and SB-277011A also attenuated the expression of fear conditioning (Swain et al. 2008).

Based upon their efficacy in animal models of reinstatement to drug-seeking behavior, selective D_3R antagonists might be considered optimal medications for the prevention of relapse in the newly abstinent substance-dependent individual across all SUD. If relapse prevention is the expected target endpoint of selective D_3R antagonists, a clinical proof of concept study could be a design in which a withdrawal phase precedes randomization to either placebo vs. the new D_3R antagonist in a blinded parallel design that would last 6–12 weeks. However, individuals who successfully quit during the withdrawal phase may decline to enter the randomization phase, and/or the rate of successful quitting (achieving abstinence) may be so small that large numbers of subjects must be enrolled for a relatively small number of subjects in the two arms of the randomization phase. These operational challenges translate into costly and unusually long trials for a proof of concept.

In contrast, human laboratory trials can model several aspects of SUD that are most relevant to selective D_3R antagonists including cue-induced craving in abstinent individuals, choice or reward paradigms, progressive ratio paradigms, and assessments of how much a subject is willing to work for a given substance in the abstinent state. These paradigms are ideal for demonstrating clinical proof of concept since they require small sample sizes, rely primarily on crossover rather than parallel designs, and are relatively short. Although these human laboratory models have been studied with various substances, their predictive validity to demonstrate clinical efficacy of a new chemical entity remains to be established.

Craving has been described as a core feature of SUD, including those associated with opioids, alcohol, nicotine, cannabis, cocaine, and other psychoactive substances

(Kakko et al. 2019). The importance of craving as both a symptom and driver of SUD has elevated the relevance of its reduction as a critical treatment target and has renewed research focus on its role in addiction treatment and relapse (Kleykamp et al. 2019). This need was recently reinforced by the US Food and Drug Administration (FDA) in a statement on the necessity for new approaches to treat OUD (Opioid-Use-Disorder 2020; Statement-from-FDA-Commissioner 2018). There is substantial evidence showing increased craving and signs of physiological arousal to drug-related vs. neutral cues in drug users. Cue-induced craving can be studied in the human laboratory and/or in combination with imaging assessments. For example, reproducible findings have been observed in cue-induced craving in newly abstinent alcoholics (Myrick et al. 2008; Wrase et al. 2008) and in abstinent smokers (Brody et al. 2007; Due et al. 2002). The effect of a new medication on these reproducible cue-induced fMRI signals could be relatively easily determined in either single or repeat dose, parallel or crossover design, using a small number of subjects and completing the trial in a relatively short time period. Recent preliminary evidence (Regier et al. 2021) also suggests that a sustained response to repeated cocaine cues within a single passive-viewing fMRI task, featuring novel evocative (cocaine, sexual, aversive) and neutral comparator cues which were repeated later, is a potential predictor of drug-use outcomes. One may therefore suggest that pharmacological interventions that would restore a normal (i.e., decreased) response to the repeated presentation of drug-associated cues in this paradigm may predict a reduction in future drug use. This hypothesis, however, warrants future studies with potential new investigational drug candidates such as selective D_3R antagonists.

Other surrogate markers might include abstinence-induced cognitive changes, such as interference on the Stroop task. For example, abstinent smokers may show altered reaction time to cigarette cues vs. neutral cues in the Stroop task, known as attentional bias induced by cues. If a compound, such as a selective D_3R antagonist, is effective in preventing cue-induced relapse it would also be expected to prevent abstinence-induced cognitive changes, many of which are cue-induced. Medication effects have been demonstrated in this paradigm (Franken 2003) using either a single or repeat dose crossover study design (Patterson et al. 2009).

Ultimately, a more suitable model for SUD might be the one typically used for major depressive disorder (MDD). That model proposes acute treatment of 4–-9 months post-clinical response for the first MDD episode, but even longer treatment for 2 or more episodes (Qaseem et al. 2008). Such a treatment paradigm is one for which selective D_3R antagonists would be uniquely suited, perhaps providing long-term relapse prevention for the highly recurrent and relapsing disorders of substance dependence.

As extensively reviewed, D_3R is highly expressed in several brain regions such as the NAc, Amy, and prefrontal cortex (including the insula) that are critically involved in reward, anxiety, and cognitive functions. A hypodopaminergic state may exist in persons living with SUD or comorbidity with MDD or AD. Thus, we propose that selective D_3R antagonists or partial agonists may be ideal for the treatment of SUD, perhaps particularly for those with MDD or AD comorbidity (Fig. 6). On the one hand, blockade of presynaptic D_3R in these brain regions may

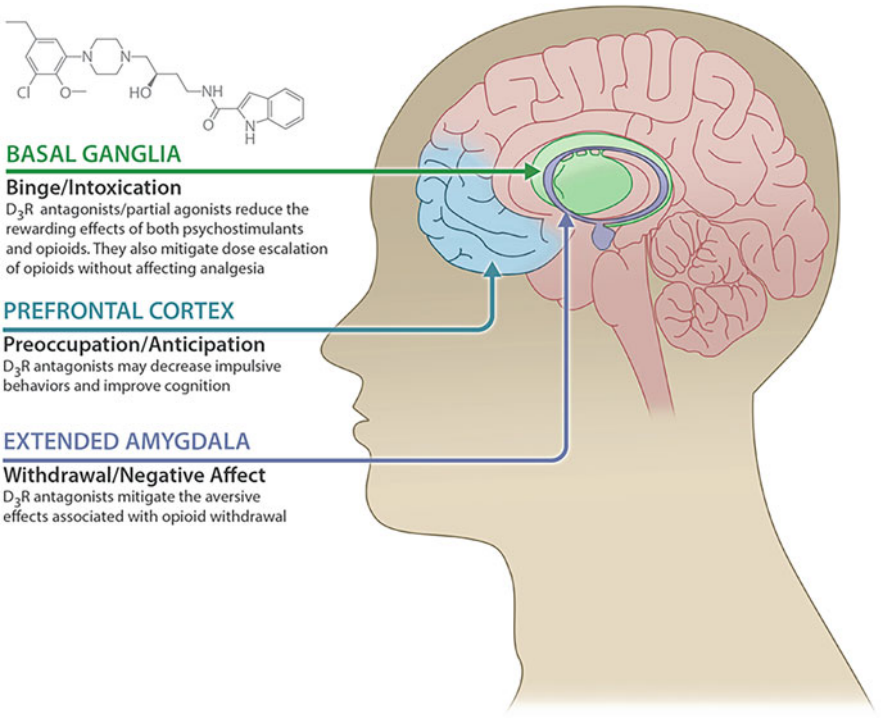

Fig. 6 Schematic diagram illustrating the major brain regions that D_3R antagonists or partial agonists may target, and the major pharmacological action produced by D_3R antagonists or partial agonists based on recent findings from preclinical and clinical studies

normalize the hypodopaminergic state, therefore relieving craving motivation for drug seeking, and improve withdrawal/negative affect and cognitive function. Conversely, blockade of postsynaptic D_3R in these brain regions may reduce the rewarding effects produced by acute use of psychostimulants and/or opioids.

4.4 From Monotherapy to Combination of Medications

The population of persons living with SUD has evolved considerably over time. Recent analyses suggest that among fatal opioid overdoses 78% involved another opioid, 21.6% involved cocaine, 11.1% involved alcohol, and 5.4% involved a psychostimulant other than cocaine (Jones et al. 2018). Polysubstance use of tobacco, psychostimulants, cannabis, or alcohol has also been observed in opioid-related emergency department visits (Liu and Vivolo-Kantor 2020), and the likelihood of these visits has been associated with the degree of severity of other SUD (John et al. 2019; Zale et al. 2015). Recent reports also indicate that

methamphetamine use is associated with a discontinuation of buprenorphine treatment in people with an OUD (Tsui et al. 2020).

Polysubstance use is therefore a considerable challenge for translational medicine and medication development. The majority of research on SUD has indeed focused on single drugs in isolation, with a multiple drug use history often considered an exclusion criterion for pivotal clinical trials. Real-world settings, however, indicate that polysubstance use is associated with poorer treatment retention, higher rates of relapse, and a three-fold higher mortality rate compared to mono-substance use (Williamson et al. 2006). This is to say that pharmacotherapy may also require multipronged rather than monotherapeutic strategies. Therefore, studies examining the efficacy of pharmacotherapy alone vs. combined medication and psychosocial counselling are required to better understand the role each treatment modality may have. Preliminary data indicate that buprenorphine + naloxone, used in combination with an extended-release injectable formulation of naltrexone may be associated with reductions in cocaine use among people who met DSM-4 criteria for cocaine dependence and past or current opioid dependence or abuse (Ling et al. 2016). Similarly, adults with methamphetamine use disorder who received extended-release injectable naltrexone plus oral extended-release bupropion over a 12-week period seemed to show a reduction in use as well (Trivedi et al. 2021). The use of long-acting injectable formulations of well-established medications for OUD in combination with new investigational drug candidates such as a D_3R antagonist/partial agonist may open new avenues to prevent reinstatement of drug-seeking and drug-taking behaviors. In addition, the D_3R antagonist/partial agonist may allow the reduction in dose of the canonical monotherapies, such as methadone or buprenorphine, and thus reduce side effects (e.g., constipation) and potential overdose.

5 Summary

The prevalence and horrific loss of life from SUD has recently been highlighted by the opioid crisis. COVID-19 has further exacerbated this societal problem. Social isolation, devastation brought on by massive loss of life, and fatigue of lives disrupted have all contributed to an increase in SUD which has then translated into >90,000 drug overdose deaths in the past year, in the USA alone. The rapidity with which vaccines and medications have been developed to treat COVID-19 demonstrates that when a crisis is taken seriously, biomedical research can in fact be translated into clinically useful treatments quickly. And yet, this same fervor has never been directed toward SUD. The sad outcome is limited or indeed no medications available to treat PSUD. Although medications to treat OUD are clinically approved, they are not always effective (Strain et al. 2021) nor universally available, especially in this time of restricted access. The need for moving new medications forward through the pipeline is far overdue. Although admittedly complicated, SUD is a serious and life-ending disorder for many. The time for advancing medications

such as the D_3R antagonists/partial agonists as monotherapies or as part of a therapeutic regimen is now. Even if these medications are only effective for a subpopulation of patients, e.g., those who suffer from comorbidities with SUD, lives will be saved, and a perfect storm may be survived.

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