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CHAPTER TWELVE

Substance abuse and neurotransmission

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Abstract

The number of people who suffer from a substance abuse disorder has continued to rise over the last decade; particularly, the number of drug-related overdose deaths has sharply increased during the COVID-19 pandemic. Converging lines of clinical observations, supported by imaging and neuropsychological performance testing, have
demonstrated that substance abuse-induced dysregulation of neurotransmissions in the brain is critical for development and expression of the addictive properties of abused substances. Recent scientific advances have allowed for better understanding of the neurobiological processes that mediates drugs of abuse and addiction. This chapter presents the past classic concepts and the recent advances in our knowledge about how cocaine, amphetamines, opioids, alcohol, and nicotine alter multiple neurotransmitter systems, which contribute to the behaviors associated with each drug. Additionally, we discuss the interactive effects of HIV-1 or COVID-19 and substance abuse on neurotransmission and neurobiological pathways. Finally, we introduce therapeutic strategies for development of pharmacotherapies for substance abuse disorders.

## Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| 5-HT         | serotonin |
| AMPAR        | α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors |
| AMPH         | amphetamine |
| DA           | dopamine |
| DAT          | dopamine transporter |
| GABA         | γ-aminobutyric acid |
| GLU          | glutamate |
| M-,K-,D-, OR | μ-, κ-, δ- receptors |
| METH         | methamphetamine |
| MSN          | medium spiny neuron |
| NAc          | nucleus accumbens |
| nAChRs       | nicotinic acetylcholine receptors |
| NE           | norepinephrine |
| NET          | norepinephrine transporter |
| NMDAR        | N-methyl-D-aspartic acid receptors |
| ROS          | reactive oxygen species |
| SERT         | serotonin transporter |
| Tat          | transactivator of transcription |
| VMAT-2       | vesicular monoamine transporter 2 |
| VTA          | ventral tegmental area |
| σ1R          | σ1-receptor |

### 1. Introduction

Substance abuse presents a significant and growing health crisis in the United States. The provisional data for the center for disease control (CDC) indicates a drastic increase of the number of overdose related deaths during the COVID-19 pandemic (Ahmad, Rossen, & Sutton, 2021). Furthermore, during the COVID-19 pandemic there has been an increase...
in the self-reported use of substances of abuse, particularly due to the increase in stressors imposed by the pandemic (Czeisler et al., 2021). The number of overdose-related deaths has continued to increase over the last 5 years, and from November 2019 through November 2020 there was a record high of 90,722 reported deaths. Importantly, a recent study found that the medical cost associated with substance abuse in 2017 was approximately $13.2 billion (Peterson, Li, Xu, Mikosz, & Luo, 2021). Understanding how these drugs of abuse impact neurotransmission is critical for addressing this health crisis. For this chapter, we review recent advances in knowledge made in understanding how commonly abused substances, including cocaine, amphetamines, fentanyl, heroin, alcohol, and nicotine, impact neurotransmission on a molecular level. We discuss the direct effects of these substances on their molecular targets, which lead to dysregulation of neuro-signaling, and their indirect (downstream) effects on neuro-signaling with the hope of highlighting potential targets for therapeutic intervention. While progression from substance abuse to addiction is a critical area of interest, the development from substance abuse to substance addiction has been discussed, and is not the primary focus for this chapter (Uhl, Koob, & Cable, 2019; Wise & Koob, 2014). This chapter will focus on the general neurochemical effects elicited by these abused substances and how they impact behavior outcomes.

Changes in neurotransmission due to abused substances will be discussed in the context of relevant neurocircuitry pathways. For instance, abused substances either directly or indirectly, alter dopaminergic transmission in the mesocorticolimbic pathway, leading to the development and expression of drug dependence. There is a debate regarding the specific direction of dopaminergic tone (increased or decreased) which is critical for developing addiction (Samaha, Khoo, Ferrario, & Robinson, 2021). Regardless, alterations in DA neurotransmission within the mesolimbic pathway are critical for mediating substance induced behaviors. The mesolimbic pathway includes dopaminergic projections from the ventral tegmental area (VTA) to the Nucleus Accumbens (NAc) (Volkow, Wang, Fowler, & Tomasi, 2012). The glutamatergic projections from the NAc to the prefrontal cortex (PFC) make up the mesocortical pathway, which is key factor for memory formation and is implicated in the long-lasting effects of drug use (Feltenstein, See, & Fuchs, 2021). Synaptic plasticity (strength of synaptic transmission) in response to acute drug use mediates the long-lasting molecular changes which store drug experience and promote relapse (Zhang & Branham, 2020). Synaptic plasticity and dysregulation of dopaminergic transmission are central to drug induced adaptations in neurotransmission signaling.
However, other neurotransmitter signaling systems are also affected, including serotonin (5-HT), norepinephrine (NE), γ-aminobutyric acid (GABA), and acetylcholine (ACh). Furthermore, the endogenous opioid system, which has direct influence on dopaminergic signaling, is also associated with susceptibility to substance abuse disorders (Butelman, Yuferov, & Kreek, 2012). These signaling systems are the most prominent direct molecular targets and downstream mediators associated with neuroadaptations in response to abused drugs.

2. Cocaine

2.1 Cocaine targets of neurotransmission

Cocaine abuse is a highly prevalent health crisis in the United States. In 2014, there was an estimated 900,000 adults nationwide living with cocaine use disorder (CUD), while in 2018 there were 19 million users worldwide (Lipari & Van Horn, 2017; United Nations Office on Drugs and Crime (UNODC), 2020). The primary driver of cocaine-induced dysregulation of neurotransmission has been attributed to the direct inhibition of the dopamine transporter (DAT) by cocaine, leading to increased extracellular DA levels (Rocha et al., 1998). Cocaine interacts with the dopamine (DA) uptake site on DATs with an inhibitory concentration in the micromolar range. However, many higher affinity DAT inhibitors do not share the behavioral response of cocaine, suggesting that cocaine may interact with DAT through alternative binding sites. A recent computational modeling study has revealed that cocaine binds to a novel high-affinity second binding site allosterically (Xu & Chen, 2020). Indeed, a recent study found that cocaine at nanomolar levels can elicit neural autophagic degradation of DAT in vitro and in vivo, suggesting a potential mechanism for how cocaine increases extracellular levels of DA despite having a weak affinity for DAT (Harraz et al., 2021). DAT function and availability are regulated by its endocytic trafficking and dynamic conformational changes (Fagan, Kearney, & Melikian, 2020). Cocaine promotes the outward-facing conformation of DAT, which was associated with reduced oligomerization of DAT and subsequently reduced endocytosis of the transporter (Sorkina et al., 2021). Thus, in the context of cocaine-mediated endocytosis of DAT, there is a need for improved tools to fully understand how cocaine regulates DAT trafficking.

In addition to DAT, cocaine has been found to directly interact with the norepinephrine (NE) transporter (NET), serotonin (5-HT) transporter (SERT), and the σ1-receptor (σ1R) (Blakely, De Felice, & Hartzell, 1994; Ravna, Sylte, & Dahl, 2003). Increased NE released from the Locus
Coeruleus (LC) as a result of cocaine inhibition of NET is thought to drive the α1b-adrenoceptor (α1-AR)-mediated increases in glutamate (GLU) transmission from the medial prefrontal cortex (mPFC), which is critical for cocaine reinstatement (Zhu et al., 2017). Cocaine induces an increase in extracellular 5-HT through inhibition of SERT, which then activates 5-HT1B receptors on D2R MSNs, consequently inhibiting GABA transmission on the GABAergic neurons in the ventral palladium (Matsui & Alvarez, 2018). Cocaine-induced alteration of serotoninergic signaling has been implicated as a key mediating factor for cocaine-induced reinforcement. Lastly, σ1R is primarily an endoplasmic reticulum protein, however, it has several roles including regulation of Ca\(^{2+}\) dynamics as well as regulation of Na\(^+\), K\(^+\), and Cl\(^-\) channels (Maurice & Su, 2009). Recent advances suggest that σ1R interacts with DA molecular targets. This includes increasing D2R function, as well as interacting directly with DAT to promote occupation of its outward-facing conformation, subsequently promoting cocaine binding (Beggiato et al., 2017; Hong et al., 2017).

### 2.2 Cocaine-induced long-lasting changes in neurotransmission

A prominent neuroadaptation driven by cocaine is the development of silent synapses, which are considered as key aspects of cocaine memories related to reinforcement and relapse. The cocaine-generated silent synapses are immature glutamatergic synapses characterized by a decreased ratio of the glutamatergic ionotropic receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) to N-methyl-D-aspartic acid receptors (NMDARs) (Dong, Taylor, Wolf, & Shaham, 2017). The cocaine-generated silent synapses are unsilenced and become matured by replacing GLUN2B subunits with GLUN2A subunits in NMDARs (Smaga, Sanak, & Filip, 2019). How cocaine induces the changes in NMDAR stoichiometry is still unclear, however, activation of D1 receptors modulating NMDAR-mediated GLU signaling presents a potential mechanism. Glutamatergic inputs from the paraventricular nucleus of the thalamus (PVT) to the NAc medium spiny neurons (MSNs) are essential in formation of the silent synapses and cocaine-related memories. These particular silent synapses are important for acquisition of cocaine self-administration but not for incubation of cocaine craving (Neumann et al., 2016). Therefore, the long-lasting incubation of cocaine is dependent on specific neurocircuitry pathways in order to store cocaine experience necessary for cocaine reinstatement. A study found that infralimbic and prelimbic medial prefrontal cortex (mPFC) inputs to the NAc also undergo silent-synapse formation in
response to cocaine. These projections undergo different unsilencing mechanisms, and more importantly, unsilencing the infralimbic to NAc projection potentiated relapse, whereas unsilencing of the mPFC to NAc inhibited cocaine craving (Ma et al., 2014). Thus, targeting the functional states of cocaine-generated silent synapses can disrupt cocaine memories and reduce cocaine-mediated behavior.

Cocaine-induced adaptive changes in neurotransmission are mediated through functional expression of D1 or D2 receptors on NAc MSNs (Zinsmaier, Dong, & Huang, 2021). Cocaine-induced silent synapses are formed at D1R MSNs and are unsilenced by recruiting AMPARs to increase AMPAR/NMDAR (Graziane et al., 2016). These NAc MSNs also differ in that D1R contain the opioid neuropeptide dynorphin (Dyn) and the D2R, enkephalin (Enk). Cocaine increases Enk levels, likely through activation of D1R and NMDAR–mediated pathways. Increased Enk can further modulate dopaminergic and glutamatergic signaling through various opioid receptor interactions, even influencing AMPA trafficking (Mongibragato, Avalos, Guzmán, Bollati, & Cancela, 2018). This evidence supports that long-lasting neuroadaptation in response to cocaine occurs in MSNs through both silent synapses and the endogenous opioid system.

Traditionally, it was believed that cocaine-induced inhibition of DAT is primarily responsible for cocaine-driven behavior (Rocha et al., 1998). However, research since has implicated multiple neuronal pathways in contributing to cocaine-driven behavior. Therefore, alternatives to targeting DAT have been developed as therapeutic approaches to treatment of CUD, including D3 receptor antagonists, 5-HT receptor agonists, and N-acetylcysteine (NIDA, 2020). To date, there are no FDA approved pharmacotherapies for treatment of CUD based on the following potential reasons: (1) There are molecular interactions between the treatment and therapeutic target outside of key neurocircuitry pathways creating off target effects; (2) Treatments only target one neurotransmitter system, which are insufficient to completely abolish drug-induced behaviors; and (3) CUD patients may take more than one substance as many drug users co-abuse psychostimulants, thereby complicating their state of dysregulated neurotransmission. For example, the orexin neuropeptide system presents a shared target in co-abused cocaine and alcohol and thus a possible avenue for therapeutic development (James, Fragale, O’Connor, Zimmer, & Aston-Jones, 2021). Understanding the effects of co-abused substance drugs on neurotransmissions and neuronal pathways will be beneficial for developing therapeutic strategies for treatment of co-abused substances.
3. Methamphetamine

3.1 Methamphetamine targets of neurotransmission

In 2017, an estimated 964,000 people had a methamphetamine (METH) use disorder in the United States (Chomchai & Chomchai, 2015; NIDA, 2019). Our earliest understanding of METH-induced dysregulation of neurotransmission involves alterations in dopaminergic signaling through inhibition of DATs (Fleckenstein, Metzger, Wilkins, Gibb, & Hanson, 1997). Further, the vesicular monoamine transporter (VMAT-2), the primary transporter in vesicle membrane responsible for reuptake of monoamines into presynaptic vesicles for storage, was implicated in driving METH-induced dysregulation of DA and behavior (Fukushima et al., 2007; Fumagalli et al., 1999). This led to our current model for METH induced dysregulation of neurotransmission in which METH inhibits reuptake of DA via the VMAT-2 thereby increasing cytosolic DA which then reverse transports through DAT and increases extracellular DA until all stored DA is depleted (Nickell, Siripurapu, Vartak, Crooks, & Dwoskin, 2014). There is evidence that supports the effects of METH on DA homeostasis are driven not only temporally but also bidirectionally by the concentration of METH (Branch & Beckstead, 2012). Additionally, METH exerts its neurotoxic effect on DA metabolism by directly inhibiting monoamine oxidase (MAO) (Mantle, Tipton, & Garrett, 1976) which leads to autoxidation of DA and generation of ROS and subsequent neurodegeneration (Meiser, Weindl, & Hiller, 2013). It has been postulated that ROS formed by drugs of abuse can regulate protein function through s-glutathionylation (GSH) modification at cysteine residues (Womersley & Uys, 2016). A recent study found indirect evidence supporting a possible mechanism in which ROS formed in response to METH promoted GSH modification of VMAT-2 to inhibit VMAT-2 function (Hedges et al., 2018). Lastly, METH interacts directly with \( \sigma_1 \)R, and recent evidence supports \( \sigma_1 \)R mediates METH effects on DA through direct interactions with DAT (Sambo et al., 2017). These findings highlight recent advances regarding METH-induced alterations of neurotransmission specific to the dopaminergic system.

In addition to the dopaminergic system, other signaling systems, including GLU, NE, and 5-HT neurotransmission, are also implicated by METH use (Ferrucci, Giorgi, Bartalucci, Busceti, & Fornai, 2013; Nordahl, Salo, & Leamon, 2003; Szumlinski et al., 2017). One possible mechanism underlying METH-induced increases in GLU transmission involves the vesicular...
glutamate transporter (VGLUT2), as heterozygous deletion of VGLUT2 reduced locomotor response to METH and attenuated METH-induced increases in DA and GLU (Shen, Chen, Marino, McDevitt, & Xi, 2021). Moreover, the metabotropic GLU receptor, mGlu5, mediates METH effects on DA dynamics and behavior. Negative allosteric modulators of mGlu5 attenuated METH effects on striatal DA and METH-conditioned place preference (Petzold, Szumlinski, & London, 2021). On the other hand, METH also increases NE levels via inhibition of both NET and pre-synaptic α-adrenergic receptors (α-ARs) (Ferrucci et al., 2019). Although METH is a potent inhibitor of NET ($K_I = 110 \text{nM}$) compared to SERT ($K_I = 31.74 \text{μM}$), persistent reductions in SERT expression are observed in METH abusers (Han & Gu, 2006; Sekine et al., 2006). Further, homozygous deletion of SERT in its knock-out mouse model shows a reduction of METH-induced locomotor activity and an increase in 5-HT levels (Igari et al., 2015). A recent meta-analysis identified that functional variants of brain derived neurotrophic factor (BDNF) and fatty acid amide hydrolase (FAAH) are significantly associated with METH abuse disorder (Guerin et al., 2021). This finding is relevant to neurotransmission, as a recent study found that BDNF plays a role mediating METH effects on serotonergic cells (Sepulveda, Manning, Gogos, Hale, & van den Buuse, 2021). These studies highlight the role of nondopaminergic systems in mediating METH abuse.

3.2 Therapeutic strategies for methamphetamine abuse

Given that METH dysregulates dopaminergic transmission by targeting DAT and VMAT2, the novel compound GZ-793A was developed, which targets both DAT and VMAT-2. GZ-793A inhibits METH-induced DA release and reduces METH-induced self-administration and reinstatement of drug seeking (Alvers et al., 2012; Beckmann et al., 2012; Horton, Nickell, Zheng, Crooks, & Dwoskin, 2013). Additionally, a new study identified that NBI-98782, a metabolite of the VMAT-2 inhibitor valbenazine, attenuated AMPH-induced DA and NE efflux and reduced AMPH-induced locomotor activity in mice (Huang et al., 2020). Targeting VMAT-2 and DAT for reducing METH-induced dysregulation of DA system presents a potential therapeutic strategy for treatment of METH abuse.

Pharmacotherapies have been tested in the clinical setting for treatment of METH dependence. A recent systematic literature review reported that stimulant agonists such as dexamphetamine and methylphenidate may show promise; however, evaluating the efficacy of pharmacotherapies is
complicated, as most METH users have co-morbidities (e.g., other drugs of abuse, depression or anxiety). Therefore, further investigation in larger sample sizes is necessary (Siefried, Acheson, Lintzeris, & Ezard, 2020). A promising clinical trial showed that a combined regimen of the antidepressant bupropion and the opioid-receptor antagonist naltrexone improved patient outcomes (% of negative-urine samples over 5–6, and 11–12 weeks) compared to placebo (13.6% vs 2.5%) (Trivedi et al., 2021). While this regimen was indeed effective and supports the use of combined pharmacotherapies for treatment, overall response was low. Future work aimed at combined pharmacotherapies which target multiple METH interactions will likely be key to developing highly effective treatment of METH dependence.

4. Amphetamine

4.1 Amphetamine targets of neurotransmission

Amphetamine (AMPH) is a structural analog of METH and is used as a prescription treatment for attention deficit hyperactive disorder (ADHD). Although METH is easier to access recreationally, the two drugs share molecular mechanisms and behavioral outcomes and are therefore often used interchangeably (Chou, Huang, & Jiann, 2015). Here, we highlight the similarities and differences between AMPH and METH impacts on behavior and neurotransmission.

Both AMPH and METH have the same mechanism underlying dysregulation of DA neurotransmission through inhibition of VMAT-2 and DAT (Carboni et al., 2001; Jones, Gainetdinov, Wightman, & Caron, 1998; Takahashi et al., 1997). Additionally, both AMPH and METH share the same nondopaminergic targets including MAOs, catechol-O-methyltransferase (COMT), SERT, and NET (Sulzer, Sonders, Poulsen, & Galli, 2005). As with METH, AMPH has a concentration dependent effect on mediating extracellular DA levels (Felmer, Janson, Summers, & Wallace, 2019; Siciliano, Calipari, Ferris, & Jones, 2014). However, METH is five times more effective than AMPH at releasing DA via efflux through DAT and inhibiting DA clearance through DAT (Goodwin et al., 2009). Homozygous deletion of DAT in mice prevented AMPH-induced locomotor activity, indicating DAT as a critical component for AMPH-induced behavior (Giros, Jaber, Jones, Wightman, & Caron, 1996). AMPH increases extracellular DA through reverse transport via DAT therefore understanding the specific mechanism for AMPH-mediated DA efflux has been a key area of interest (Kahlig et al., 2005). Early evidence indicated roles for both
intracellular Ca\(^{2+}\) and physical association with protein kinase C\(\beta\) (PKC\(\beta\)) in mediating DA efflux through DAT (Johnson, Guptaroy, Lund, Shamban, & Gnegy, 2005). In agreement with this, phosphorylation of DAT by AMPHs specifically (not cocaine) by PKC\(\beta\) was crucial for promoting AMPH-induced DA efflux though DAT (Foster et al., 2012). Evidence supports that other proteins and molecules including syntaxin 1A, G protein \(\beta\gamma\) (G\(\beta\gamma\)) subunits, and phosphatidylinositol (4,5)-bisphosphate (PIP\(_2\)) help to facilitate AMPH-induced DA efflux through DAT (Belovich et al., 2021; Binda et al., 2008; Mauna et al., 2019). Further, recent evidence has also identified the organic cation transporter 3 (OCT3), which non-selectively transports monoamines, as another transporter protein which undergoes AMPH-induced DA efflux (Mayer et al., 2018). Understanding the molecular mechanism for AMPH-induced DA efflux through DAT may identify novel therapeutic targets for alleviating AMPH-induced behavior (Sitte & Freissmuth, 2015).

AMPH also dysregulates non-dopaminergic forms of neurotransmission. AMPH-induced conditioned place preference and locomotor activity are dependent on functional expression of NET (Mannangatti, R. Ramamoorthy, & Jayanthi, 2018). Pharmacological evidence supports that AMPH-stimulated NE release may contribute to AMPH-induced behavior (Rothman et al., 2001). In addition to NE, AMPH also increases GLU transmission. Increased GLU levels may be a result of endocytosis of the GLU transporter. AMPH-induced endocytosis of EAAT3 is mediated by the trace amine–associated receptor, TAAR1 (Underhill, Colt, & Amara, 2020; Wolf, Xue, Li, & Wavak, 2000). In addition to EAAT3, the major GLU transporter GLT-1 also mediates AMPH-induced behavior. AMPH-induced locomotor activity was reduced in conditional GLT-1 KO mice (Fischer et al., 2018). Another study found that AMPH did not induce changes in GLT-1 expression in the mPFC or NAc. However, this study found that \(\beta\)-lactam antibiotic ceftriaxone, which restores GLT-1 expression, reduced AMPH-induced drug seeking and cue-induced reinstatement of drug seeking behavior (Garcia, Arndt, & Cain, 2019). AMPH-induced dysregulation of non-dopaminergic neurotransmission is an important area of research which warrants further exploration.

### 5. Opioids

Persistent pain affects nearly 100 million adults in the United States, with an economic cost between $560 and $635 billion annually (Gaskin & Richard, 2012). The overuse of opioids prescribed for pain has
led to the prevalence of opioid use disorder (OUD), and in recent years, is linked to the increased use of cheaper illicit opioids such as heroin and fentanyl (Stoicea et al., 2019), which accounted for 66.4% of all overdose deaths in 2016 (Seth, Scholl, Rudd, & Bacon, 2018). Development of pharmacotherapies are not only critical for treatment of ongoing OUD, but non-addictive opioid alternatives as pharmacotherapy for pain management is crucial in mitigating the development of OUD. For the purposes of this review, we will focus on ongoing developments related to the molecular mechanism of illicit opioids of abuse.

5.1 Opioid targets of neurotransmission

Opioids include a class of drugs used for treatment of pain that act at opioid receptors including μ-(MOR), κ-(KOR), and δ-(DOR) receptors (Sun, Chen, Chen, & Pan, 2019; Wang, 2019). Differential localization of opioid receptors throughout the CNS have been characterized and attributed to the receptor-specific effects of mediating analgesia (inability to feel pain), dysphoria (unease), and other autonomic functions, and is detailed further in review (Valentino & Volkow, 2018). Additionally, how interactions between the opioid morphine and addiction related pathways has been extensively discussed in a recent review (Kupnicka et al., 2020). For the purposes of this chapter, we will focus on fentanyl and heroin effects on neurotransmission.

5.2 Fentanyl

Fentanyl is typically used for treatment of patients with severe pain; however, the illicit use of fentanyl has increased over the past several years (Hedegaard, Minino, & Warner, 2018). Recent evidence shows an increase in the incidence of fentanyl-related overdose deaths (Davis & Behm, 2020). Fentanyl is a powerful synthetic opioid analgesic that is similar to morphine but has high lipophilicity and is 100 times more potent as a high affinity agonist for MOR compared to other opioid receptors (DOR, KOR) (Maguire et al., 1992). Recently, the binding mode of fentanyl to MOR has been characterized (Vo, Mahinthichaichan, Shen, & Ellis, 2021). Fentanyl acts as a biased agonist of MOR to promote a unique signaling cascade through activation of MOR, which favors downstream signaling through β-arrestin-2 over G-protein signaling (Comer & Cahill, 2019). Neurochemical effects of fentanyl include dysregulation of DA, GLU, and GABA transmission. Fentanyl increases DA in the NAc through activation of MOR and DOR (Yoshida et al., 1999). Interestingly, a recent study found that treatment with a growth hormone secretagogue receptor (GHS-R1A) antagonist reduced fentanyl-induced
increases in DA in the NAc and reduced fentanyl–conditioned place preference in rats (Sustkova-Fiserova et al., 2020). The mechanism by which GHS–R1A mediates fentanyl effects on neurotransmission is still under investigation. Fentanyl also dysregulates GLU and GABA transmission, as has been previously observed in the peripheral nervous system (Fu, Tsen, Lee, Lui, & Chan, 1997; Griffioen et al., 2004). A recent study found that fentanyl increased GABA release and decreased GLU release in the anterior hypothalamus of rats (Pourzitaki et al., 2018). How fentanyl reduces GLU release is not fully understood, however, endogenous opioids have been shown to act in a retrograde manner to inhibit excitatory transmission thereby presenting a possible mechanism for this phenomenon (Iremonger & Bains, 2009).

The MOR antagonist naloxone is the primary treatment for opioid overdose (Baumann, Kopajtic, & Madras, 2018). Converging lines of evidence have found that repeated administration of naloxone is needed in fentanyl-related overdoses, in part due to the short half-life (30–90 min) of naloxone (Faul et al., 2017; Somerville et al., 2017). However, it is not entirely clear why multiple doses of naloxone are needed. There is evidence that respiratory complications arise during fentanyl-related overdoses specifically (Fairbairn, Coffin, & Walley, 2017). These respiratory complications, referred to as “wooden chest syndrome,” cause muscle rigidity which occurs quickly (within 2 min) (Pergolizzi, Webster, Vortsman, Ann LeQuang, & Raffa, 2021). Early evidence regarding the pharmaceutical action of fentanyl suggested the role of NE and cholinergic systems in mediating fentanyl off target effects (Atcheson, Rowbotham, & Lambert, 1993). This is of interest, as recent evidence suggests a possible role for these systems in mediating fentanyl-related respiratory and cardiovascular failure (Torralva & Janowsky, 2019). Further research to improve the treatment of fentanyl-related overdoses is warranted (Comer, Pravetoni, Coop, Baumann, & Cunningham, 2021; Pergolizzi et al., 2021; Volkow, 2021). Improving the efficacy of treatment administered will likely improve the survival outcome of those experiencing a fentanyl-related overdose. This would be particularly beneficial in rural areas, where emergency response times are longer (Faul et al., 2017), and bystander intervention is necessary to swiftly treat the patient (Somerville et al., 2017). In addition to naloxone, targeting the effects of fentanyl on NE and cholinergic systems presents one possible approach for improving therapeutic treatment of fentanyl-related overdoses.

Lastly, recent in vitro evidence supports possible interaction between fentanyl and several non-MOR targets involved in neurotransmission. Fentanyl binds 5-HT receptors (5-HT_{1A} and 5-HT_{2A}), acting as an agonist at 5-HT_{1A},
and produces efflux of 5-HT (Baldo & Rose, 2020). Furthermore, a recent pharmacological study was done to identify potential non-MOR molecular targets for fentanyl. This study found in vitro evidence which supports several possible non-MOR interactions for fentanyl. This includes binding of fentanyl to NE receptors (α1-ADr), weak inhibition of uptake through at DAT, SERT, and NET, partial antagonist action at DA receptors (D4.4), and inhibition of uptake through VMAT-2 (Torralva et al., 2020). Future in vivo work is necessary to validate these molecules as molecular targets for fentanyl and to determine whether these interactions contribute to fentanyl-induced behaviors.

5.3 Heroin

Heroin use in the United States has continued to increase since 2000 and in 2015 the societal cost of heroin use disorder was an estimated $51.2 billion (Jiang, Lee, Lee, & Pickard, 2017). Heroin is a prodrug form of morphine that is readily metabolized into 6-monoacetylmorphine (6-MAM) and morphine (Rook, Huitema, van den Brink, van Ree, & Beijnen, 2006; Sawynok, 1986). Heroin acts as a highly addictive analgesic drug through interaction with MORs (Wang et al., 2016). The long-standing hypothesis of opioid reward is that opioid activation of MORs in GABAergic interneurons in the VTA disinhibits dopaminergic neurons thereby increasing DA in the reward pathway (Corre et al., 2018). However, this model has been repeatedly challenged. Early evidence found that MORs are expressed throughout the VTA and heroin is self-administered in the absence of DA terminals (Pettit, Ettenberg, Bloom, & Koob, 1984). A recent study found that conditional KO mice lacking MOR in the striatum had no locomotor response and reduced motivation to heroin; however, heroin-conditioned place preference remained intact (Charbogne et al., 2017). Further, another study found that inhibition and activation of MORs in the substantia nigra had a greater impact on reducing, and reinstating (respectively) drug seeking behavior in response to heroin compared to GABAergic VTA neurons (Galaj et al., 2020). This evidence supports a role for MORs in regions besides the VTA for promoting heroin-induced behaviors.

Although the relationship between MORs and the reward pathway is not fully elucidated, there is evidence which indicates heroin use is associated with dysregulation of dopaminergic and serotonergic function. For instance, DAT expression is increased in early heroin addicted rat models and decreased availability of DAT was observed in heroin users using
PET scan imaging (Li, Xia, Li, Yin, & Liang, 2017; Xu et al., 2017). As well, genetic variants of DA receptors (Lachowicz et al., 2020; Zhan et al., 2018) as well as serotonergic molecules, appear to correlate with heroin dependence (Cao, LaRocque, & Li, 2013; Yin et al., 2016). However, whether heroin alters dopaminergic and serotonergic function remains controversial. Single photon emission computed tomography (SPECT) showed no difference in DAT and SERT levels between healthy individuals and heroin users (Cosgrove et al., 2010). Therefore, more work is needed to discern the impact of heroin on DA and 5-HT signaling.

Glutamatergic function is associated with heroin relapse (Knackstedt & Kalivas, 2009). GLU release in the NAc core of rats is necessary for heroin seeking, which can be blocked by inhibition of AMPA receptors (LaLumiere & Kalivas, 2008). As previously discussed in the cocaine section, generation of silent synapses are thought to be key to storing cocaine experience, and unsilencing these synapses is key for reinstatement of drug seeking behavior. Cocaine forms silent synapses on D1R-MSNs by increasing NMDARs containing the GLUN2B subunit whereas morphine preferentially forms silent synapses on D2R-MSNs by insertion of AMPARs. Unsilencing of synapses for cocaine involves strengthening of D1R by insertion of AMPARs, whereas morphine involves removal of AMPARs on D2R-MSNs. Although the mechanism for unsilencing synapses differs between morphine and cocaine, both drugs lead to an increase in D1R/D2R-MSN synapses (Hearing, Graziane, Dong, & Thomas, 2018). Heroin also impacts astrocytic function (Reynolds, Mahajan, Sykes, & Nair, 2006), thereby mediating heroin’s effects on GLU levels, as astrocytes are important for mediating for the glutamate-glutamine cycle. Heroin induces dynamic changes in expression of the GLU transporter GLT-1 in NAc astrocytes, and the role of plasticity in specific astrocytic populations in mediating heroin-seeking behavior is an ongoing area of research (Kruyer & Kalivas, 2021). Molecules involved in GLU function may yield possible therapeutic targets for treatment of heroin-induced relapse.

5.4 Pharmacotherapies for opioid abuse

Three types of FDA approved treatments are available for OUD: buprenorphine, a partial MOR agonist and KOR antagonist; naltrexone, an opioid receptor antagonist; and methadone, an MOR agonist (Helm, Trescot, Colson, Sehgal, & Silverman, 2008). Despite this, financial and regulation barriers remain and have prevented universal accessibility to these
treatments (Meyer, 2020; Sharma et al., 2017). Furthermore, because buprenorphine and methadone act as agonists there is the potential for development of withdrawal symptoms, therefore these drugs are often prescribed below the minimal dosage required to be effective (Volkow, Jones, Einstein, & Wargo, 2019). While these drugs focus on treatment of OUD, another MOR high affinity antagonist, naloxone, is the primary treatment for opioid overdose (Chou et al., 2017; Wang, Frankfurt, & Burns, 2008). There is indeed evidence of the benefits of naloxone in the reversal of opioid overdose, however, similar to that of treatments for OUD, the barriers are in place regarding naloxone access which need to be addressed (Behar, Bagnulo, & Coffin, 2018; Smart, Pardo, & Davis, 2021).

6. Alcohol

6.1 Alcohol-mediated effects on neurotransmission

According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) there were 14.1 million adults and 414,000 adolescents who had an alcohol use disorder (AUD) in 2019 (NIAAA, 2021). Alcohol differs from the previously discussed drugs of abuse in that to date, there is no consensus that alcohol (ethanol) has a specific molecular target for which it binds and mediates dysregulation of neurotransmission. Evidence that supports potential direct molecular targets of ethanol is detailed in review, with possible direct targets including alcohol dehydrogenase (ADH), nicotinic acetylcholine receptors (nAChR), glycine receptors (GlyR), GABA receptors, NMDARs, Ca\(^{2+}\)-activated K\(^+\) (BK channels), G-protein-coupled inwardly rectifying K\(^+\) channels (GIRK), and indirect targets primarily consisting of downstream signaling factors, genetic regulators, and σ1Rs (Abrahao, Salinas, & Lovinger, 2017; Quadir, Cottone, & Sabino, 2019).

Glutamate transmission is differentially affected across the CNS in response to acute and chronic alcohol use. Molecular targets in the glutamatergic system, including ionotropic and metabotropic receptors, may present potential therapeutic targets for treatment of AUD (Burnett, Chandler, & Trantham-Davidson, 2016; Joffe, Centanni, Jaramillo, Winder, & Conn, 2018; Johnson & Lovinger, 2020). Antagonism of the metabotropic GLU receptor, mGluR5, prevented alcohol induced relapse in rats (Adams, Short, & Lawrence, 2010). Recent advances using positron emission tomography (PET) imaging have identified a link between mGluR5 availability (specifically cortical and mesolimbic) and long-term relapse in patients who abuse alcohol (Ceccarini et al., 2020; Joo et al., 2021). Additionally, acute
alcohol use inhibits the ionotropic GLU receptor NMDAR while chronic alcohol use upregulates NMDAR function. Changes in NMDAR function are important as downstream signaling pathways activated by NMDARs influence synaptic plasticity and alcohol-related behaviors (Morisot & Ron, 2017). Lastly, dysregulation of glutamatergic transmission is a key area of interest regarding co-abuse of cocaine and alcohol. Alcohol and cocaine individually increase GLU levels in the NAc through downregulating expression of the GLU transporter, GLT-1 (Fischer, Houston, & Rebec, 2013; Gass & Olive, 2008; Sari & Sreemantula, 2012), however, the effects of cocaine and alcohol effects on GLT-1 expression are nonadditive (Hammad, Althobaiti, Das, & Sari, 2017; Stennett, Padovan-Hernandez, & Knackstedt, 2020). Understanding the role of glutamatergic molecules in mediating alcohol and alcohol/cocaine abuse is of interest for future investigation.

An important polysubstance abuse cohort to consider is those who abuse alcohol and nicotine. People who smoke are 10 times more likely to abuse alcohol, and conversely an estimated 70–80% of alcoholics smoke (Cross, Lotfipour, & Leslie, 2017). Indeed, alcohol and nicotine share molecular mechanisms for acquiring self-administration (Li, Volkow, Baler, & Egli, 2007) and the mechanisms for nicotine specifically are discussed in the next section. Alcohol exploits the dopaminergic reward system by increasing DA in the NAc to drive alcohol seeking behavior, however, polymorphisms of DA molecular targets are not highly associated with AUD (Bhaskar & Kumar, 2014; Ma & Zhu, 2014). Instead, alcohol effects on dopaminergic reward pathways are mediated by interactions with nicotinic receptors (nAChRs) (Miller & Kamens, 2020). Activation of nAChRs activates DA release by increasing firing of dopaminergic neurons in the VTA, which is regulated by different nAChR subunit compositions (Mameli-Engvall et al., 2006). How nAChRs modulate alcohol and nicotine induced behaviors, respectively, is detailed in review (Miller & Kamens, 2020; Wittenberg, Wolfinan, De Biasi, & Dani, 2020). Future work should consider nAChRs as a highly probably mediator underlying polysubstance abuse of alcohol and nicotine and as a potential therapeutic target for alleviating co-morbid abuse of alcohol and nicotine.

6.2 Pharmacotherapies for alcohol use disorder

Current FDA-approved medications for treating AUD include naltrexone (general opioid receptor antagonist), disulfiram (acetaldehyde dehydrogenase inhibitor), and acamprosate (NMDA receptor antagonist, positive
allosteric GABA<sub>A</sub> modulator) (Castrén, Mäkelä, & Alho, 2019). Naltrexone is significantly effective in reducing alcohol relapse to heavy drinking, however, the degree of its effectiveness is minimal (Kranzler & Soyka, 2018; Palpacuer et al., 2018). A current approach for treatment of AUD is the development of selective KOR antagonists (Banks, 2020). Activation of KOR by the endogenous opioid peptide dynorphin (Dyn) inhibits dopaminergic firing. Acute and chronic alcohol use increases Dyn released from the D1R NAc MSNs, leading to upregulation of KOR function. How KOR function mediates alcohol-induced behavior varies based on the model used (Karkhanis & Al-Hasani, 2020; Karkhanis, Holleran, & Jones, 2017). Further research is needed to understand how KOR mediates alcohol induced behaviors for the development of KOR based therapeutic treatment of AUD.

7. Nicotine

7.1 Nicotine targets of neurotransmission

Nicotine, through activation of neuronal nicotinic acetylcholine receptors (nAChRs) in the brain (Dani, Jenson, Broussard, & De Biasi, 2011), triggers the release of several neurotransmitters including DA, acetylcholine (ACh), Glu, 5-HT, and epinephrine (Schmidt, Rupprecht, & Addy, 2019). Repeated nicotine exposure in smokers causes a number of neuroadaptations, including persistent desensitization of the predominant α<sub>4</sub>β<sub>2</sub> nAChRs (Bertrand & Terry, 2018; Feduccia, Chatterjee, & Bartlett, 2012; Zoli, Pucci, Vilella, & Gotti, 2018), strengthening glutamatergic synapses onto dopaminergic neurons (Mao, Gallagher, & McGehee, 2011; Saal, Dong, Bonci, & Malenka, 2003), altering midbrain GABAergic circuitry (Grilli et al., 2012) and upregulating D2 DA receptors in the NAc (Novak, Seeman, & Le Foll, 2010). These neuroadaptations have a great impact on diverse neurotransmissions in the mesocorticolimbic pathway, which contribute to the pathophysiology of smoking behavior and nicotine addiction. Similar to all drugs of abuse, nicotine activates β2-containing nAChRs expressed on dopaminergic neurons (Mameli-Engvall et al., 2006) and possible α7 nAChRs expressed on glutamatergic afferents (Mansvelder & McGehee, 2000) in the VTA and subsequently results in DA release in the NAc (Di Chiara, 2000; Laviolette & van der Kooy, 2004). Dopaminergic transmission has been strongly implicated in the reinforcing and withdrawal effects of nicotine, evidenced by (1) alteration of DA transmission within the mesolimbic reward system by systemic administration of nicotine and
during nicotine withdrawal (Di Chiara, 2000; Natividad, Tejeda, Torres, & O’Dell, 2010) and (2) reducing the reinforcing effects of nicotine by blocking DA receptors (Diaz et al., 2000; Liu et al., 2010). Furthermore, bupropion and varenicline that are clinically used for treatment of nicotine dependence are associated with targeting dopaminergic neurotransmission (Ericson, Löf, Stomberg, & Söderpalm, 2009; Paterson, 2009; Prochaska & Benowitz, 2016). Considering that glutamatergic transmission plays a crucial rule in the reinforcing effects of nicotine, there is growing interest in glutamate-based therapeutic strategies (Liechti & Markou, 2008). The underlying mechanism is that following administration of nicotine, activation of GLU receptors on dopaminergic neurons in the VTA by released GLU increases firing of VTA dopaminergic neurons, leading to DA release in the NAc and nicotine reward (Grillner & Svensson, 2000). Several animal studies show that nicotine-induced DA release can be reduced by administering GLU receptor antagonists (Fu, Matta, Gao, Brower, & Sharp, 2000) and GLU receptors are decreased during nicotine withdrawal (Dravolina et al., 2007; Mansvelder & McGehee, 2000). These findings suggest that therapeutic targeting glutamatergic transmission could be beneficial to smoking-cessation.

The activity of the VTA dopaminergic transmission is regulated by local GABA-releasing neurons and GLU-releasing neurons (Morales & Margolis, 2017). GABAergic transmission displays an inhibitory effect on the activation of mesolimbic dopaminergic neurons, which reduces nicotine reward and reinforcement. Acute nicotine exposure increases GABA release from the VTA GABAergic neurons, whereas chronic nicotine exposure decreases the nicotine-induced GABA release by desensitizing β2-containing nAChRs, leading to reduced inhibition of VTA dopaminergic neurons and enhanced DA release in the NAc (Mansvelder, Keath, & McGehee, 2002). The effect of GABAergic activity on nicotine reward and reinforcement is evidenced by systemic administration of GABA$_B$ receptor agonists (Fattore et al., 2009; Franklin et al., 2009; Vlachou et al., 2011). Given that DA is a precursor of NE, the stress-induced nicotine-seeking during withdrawal is mediated by NE transmission (Mantsch, Baker, Funk, Lê, & Shaham, 2016), evidenced by the stress-induced reinstatement of nicotine seeking which can be attenuated by activation of α2 adrenergic receptors (Zisls, Desai, Prado, Shah, & Bruijnzeel, 2007). In addition, recent studies show that 5–HT receptors are involved in nicotine seeking (Fletcher et al., 2012; Schmidt et al., 2019). In addition to these traditional neurotransmitters, emerging evidence shows that many neuropeptide systems such as KOR
hypocretin and corticotropin-releasing factor are related to stress-induced nicotine reinforcement and reinstatement (Bruijnzeel, 2017). These findings may provide novel preventive strategies for smoking cessation.

8. Drugs of abuse and HIV-1

HIV-1-associated neurocognitive disorders (HAND) are highly prevalent in the era of efficacious combination antiretroviral therapies (cART), with a greater number of HIV-infected persons living longer (Heaton et al., 2010, 2011). Drugs of abuse, such as METH and cocaine have been shown to increase the incidence of HAND, exacerbate its severity, and enhance viral replication (Nath, Maragos, Avison, Schmitt, & Berger, 2001; Soontornniyomkij et al., 2016). Perturbation of dopaminergic neurotransmission has been demonstrated as a mediating factor in HAND in concurrent drug abusers (Berger & Arendt, 2000; Gaskill et al., 2009; Gaskill, Miller, Gamble-George, Yano, & Khoshbouei, 2017; Purohit, Rapaka, & Shurtleff, 2011). HIV-1 viral proteins are associated with the persistence of HIV-related neuropathology and subsequent neurocognitive impairments observed in HAND (Brack-Werner, 1999; Frankel & Young, 1998; Gaskill et al., 2009; Johnston et al., 2001; Power et al., 1998). Persistent viral replication and expression of HIV-1 viral proteins within the CNS can accelerate damage in the mesocorticolimbic DA system (Berger & Arendt, 2000; Koutsilieri, Sopper, Scheller, ter Meulen, & Riederer, 2002; Nath, Jankovic, & Pettigrew, 1987) and to the brain pathways controlling motivation (Berridge, 2007; Everitt & Robbins, 2005; Wise & Bozarth, 1987). Therapy-naïve HIV patients display increased levels of DA and decreased DA turnover in the early stages of HIV infection (Scheller et al., 2010) which may initiate compensatory mechanisms eventually resulting in decreased DA levels (Kumar et al., 2009; Kumar, Ownby, Waldrop-Valverde, Fernandez, & Kumar, 2011; Sardar, Czudek, & Reynolds, 1996) and dopaminergic neuron damage (Chang et al., 2008; Wang et al., 2004) in the advanced stages of HIV infection. Importantly, the HIV-induced elevated DA level in CNS of HIV-infected patients can stimulate viral replication in human macrophages within DA-rich brain regions (Gaskill, Calderon, Coley, & Berman, 2013; Gaskill et al., 2009; Gaskill, Yano, Kalpana, Javitch, & Berman, 2014), which has been implicated in the pathophysiology of HAND (Li, Li, Steiner, & Nath, 2009).
Among the HIV viral proteins, the transactivator of transcription (Tat) protein plays a crucial role in viral replication in the early stage of HIV infection and the pathophysiological effects on development of HAND (King, Eugenin, Buckner, & Berman, 2006; Rappaport et al., 1999), as Tat protein has been detected in dopaminergic-rich brain areas (Del Valle et al., 2000; Hudson et al., 2000; Lamers et al., 2010) and in the sera (Westendorp et al., 1995; Xiao et al., 2000) of HIV-1 infected patients (Johnson et al., 2013). Our published work has demonstrated that Tat protein induces dysregulation of dopaminergic neurotransmission by inhibiting DA transport through DAT in cells expressing human DAT (Midde et al., 2013, 2015; Quizon et al., 2016), multiple HIV-1 viral protein transgenic rat model (Zhu et al., 2016), and HIV-1 Tat transgenic mouse model (Strauss et al., 2020). Notably, studying single Tat protein would allow us to identify protein targets for Tat binding and develop therapeutic approaches to prevent Tat-mediated neurological damages. Moreover, studying single Tat protein will provide insight into fully understanding the consequence of combined neurological effects of the viral proteins on the CNS. Recent studies show that other viral proteins, such as gp120 and Nef, can also influence DAT activity (Acharjee et al., 2014; Hu, Sheng, & Rock, 2013). On the other hand, clinical observations have demonstrated that DAT activity is dramatically reduced in HIV-infected patients, which is exacerbated in cocaine abusers (Chang et al., 2008; Wang et al., 2004). Interplay of Tat and cocaine augments synaptic DA release by inhibiting DAT activity (Ferris, Frederick-Duus, Fadel, Mactutus, & Booze, 2009; Zhu, Mactutus, Wallace, & Booze, 2009), which may be consistent with animal study that the transgenic expression of Tat in the mouse brain potentiates cocaine reward (Paris et al., 2014). The underlying mechanism of the Tat-induced inhibition of DAT-mediated DA reuptake is through Tat binding to allosteric binding site(s) on DAT, not by interacting with the DA uptake site (Yuan et al., 2015; Zhu et al., 2009; Zhu, Ananthan, Mactutus, & Booze, 2011). Furthermore, given that DAT-mediated DA transport process is dynamically regulated by three typical conformational states: Outward-open → Outward-occluded → Inward-open, cocaine and Tat protein prefer the outward-open state that causes inhibition of DA uptake (Yuan, Huang, Zhu, & Zhan, 2016). This mechanism has been validated by a novel DAT allosteric modulator which attenuates Tat-induced inhibition of DAT-mediated DA transport (Sun et al., 2017). Thus, developing allosteric modulators that decrease the affinity and maximal binding potential of Tat could be a viable approach for reversing Tat-induced dysregulation of the DA system.
9. Considerations regarding COVID-19

The topic of long-term COVID-19 effects on neuropsychiatric symptoms is an emerging field of great interest. While there is evidence of depression and neuroinflammation due to COVID-19, it has been reported that there is potential interplay between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and neurotransmission, such as dopaminergic and serotonergic systems (Attademo & Bernardini, 2021; Boldrini, Canoll, & Klein, 2021). This is due to the discovery that angiotensin 1 converting enzyme 2 (ACE2), a host receptor for SARS-CoV-2, is co-expressed with dopa decarboxylase (DDC), a major enzyme in the DA and 5-HT synthesis pathways (Nataf, 2020). Furthermore, a new study reports that dopaminergic neurons derived from human pluripotent stem cells are susceptible to SARS-CoV-2 infection (Chen et al., 2021). Dysregulation of dopaminergic and serotonergic systems is critical for the development of substance abuse disorders. As described in the previous section, HIV-1 induces neuropathological changes in dopaminergic signaling which increases susceptibility to development of substance abuse disorders. Based on emerging evidence and our published work from comorbidity of HIV-1 and substance abuse, we hypothesize that COVID-19 infection may induce neuropathological changes which impact neurotransmission, such as dysregulation of dopaminergic and serotonergic systems, which may greatly impact susceptibility to development of substance abuse disorders as well as neurocognitive impairments. We anticipate that the long-term impact of COVID-19 on neurotransmission will be an important area of interest requiring further research.

10. Conclusion

In this chapter, we discuss recent advances made in understanding how commonly abused substances, including cocaine, amphetamines, opioids, alcohol, and nicotine, impact neurotransmission on a molecular level. Every abused substance covered in this chapter impacts more than one neurotransmitter system, and each system plays a role in mediating certain elements of drug induced behaviors. For instance, GLU signaling generally underlies reinstatement of drug seeking, whereas dopaminergic signaling is key for acute self-administration. Abused substances induce dysregulation of neurotransmission in key neurocircuitry pathways, which act together in concert to invoke a range of drug taking behaviors. Future work is needed
to understand the impact of co-abused substances on neurotransmission. Molecular factors which mediate dysregulation of neurotransmission for more than one substance of abuse should be investigated as possible therapeutic targets for polysubstance abuse cohorts (e.g., nAChRs for alcohol/nicotine users). Translational research which integrates basic sciences and clinical observations on the neurobiological processes induced by these substances will aid in the development of effective therapeutic strategies for treatment of substance abuse disorders.

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Conflict of interest
The authors have no conflicts of interest to declare.

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