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REVIEW ARTICLE
Nanoparticle delivery systems for substance use disorder

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Innovative breakthroughs in nanotechnology are having a substantial impact in healthcare, especially for brain diseases where effective therapeutic delivery systems are desperately needed. Nanoparticle delivery systems offer an unmatched ability of not only conveying a diverse array of diagnostic and therapeutic agents across complex biological barriers, but also possess the ability to transport payloads to targeted cell types over a sustained period. In substance use disorder (SUD), many therapeutic targets have been identified in preclinical studies, yet few of these findings have been translated to effective clinical treatments. The lack of success is, in part, due to the significant challenge of delivering novel therapies to the brain and specific brain cells. In this review, we evaluate the potential approaches and limitations of nanotherapeutic brain delivery systems. We also highlight the examples of promising strategies and future directions of nanocarrier-based treatments for SUD.

INTRODUCTION

Substance use disorder (SUD) is a devastating brain disease that inflicts enormous emotional and economic cost to the individual, families, and society [1, 2]. Despite the clinical importance of limiting the development of drug craving and relapse, relatively few pharmacological treatments for SUD have received FDA approval within the last 20 years [3, 4], and currently there are no approved medications for cocaine, methamphetamine, and cannabis use disorders. Although researchers have identified many validated targets in preclinical studies [5], most large pharmaceutical companies show little interest in developing and testing novel SUD treatments [6]. Another major factor that limits therapeutic innovation for SUD and other neuropsychiatric disorder is the lack of methods to safely and effectively deliver therapeutic molecules to the brain. The brain is protected by the blood-brain barrier (BBB), which excludes large-molecule therapeutics and the vast majority of small-molecule drugs [7]. Furthermore, brain regions that drive drug craving and relapse are anatomically and functionally heterogeneous, creating a growing need for treatments that target specific cell types [8]. Thus, improvements in neurotherapeutic delivery systems are required to effectively treat SUD.

For many years in neuroscience research, the use of viral vectors has been the primary method to label and manipulate specific brain cells and circuits [9]. While viruses are excellent tools to study the brain in preclinical SUD models, limitations such as inadequate brain penetration following systemic delivery, constitutive expression, potential immune response, and cargo size restrictions have diminished the clinical utility of viral vectors as a SUD therapeutic [10]. On the other hand, non-toxic, biocompatible nanocarrier systems have emerged as a potential strategy to address the challenges of brain delivery that have hindered the advancement of many SUD treatments. As a putative therapeutic approach for SUD, nanoparticle delivery systems have several advantages, including 1) diverse therapeutic delivery applications

(nucleic acid-based agents, peptides, proteins, small molecules, etc.), 2) tunable release rate lasting several days, 3) biocompatible and relatively low toxicity, 4) brain penetrating properties due to small size and stealth coating, and 5) adaptable to surface modifications for cell type-specific delivery [11] (Fig. 1). Additionally, several nanoparticle formulations have recently received FDA approval, further supporting their safety and efficacy in a variety of diseases [12]. In this review, we highlight advances in brain-targeted nanoparticle technologies and discuss ongoing and future directions of nanoparticle delivery systems for the treatment of SUD. Importantly, non-nanoparticle therapeutic delivery techniques such as new viral vectors [13, 14], genetically modified skin grafts [15], and ultrasound-mediated drug delivery [16] are also promising treatment strategies for SUD, and these and other approaches are summarized in previously published manuscripts [17–20].

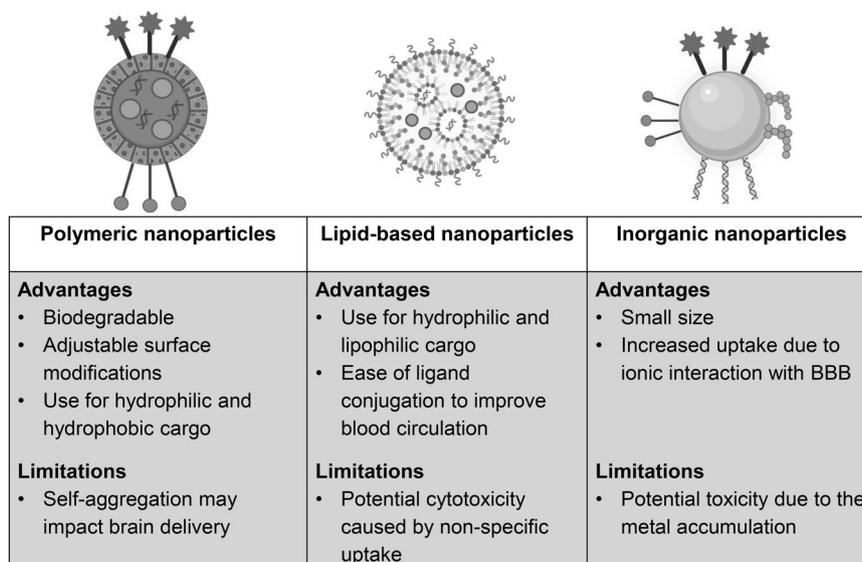## TYPES OF NANOPARTICLES FOR BRAIN DELIVERY
Polymeric nanoparticles

Biodegradable polymeric nanoparticles have diverse drug delivery capabilities making them well suited for brain-targeted applications [21] (Fig. 1). Formulated from natural and synthetic polymers, polymeric nanoparticles are able to encapsulate therapeutics agents ranging from small molecules to biologic macromolecules [22]. An advantage of polymeric nanoparticles is that the polymer composition and surface properties may be adjusted to control the release rate and promote cell type-specific delivery of the therapeutic contents [23, 24]. In preclinical models, multiple polymeric nanoformulations have been successfully tested for brain delivery applications, including but not limited to polyamidoamine (PAMAM), Poly-lactic-co-glycolic acid (PLGA), polylactic acid (PLA), polylactic acid hyperbranched polyglycerol (PLA-HPG), and chitosan [25–28]. PAMAM-bound siRNAs, for example, showed greater efficacy and accumulation in the brain compared to the free

Polymeric nanoparticles	Lipid-based nanoparticles	Inorganic nanoparticles
Advantages • Biodegradable • Adjustable surface modifications • Use for hydrophilic and hydrophobic cargo	**Advantages** • Use for hydrophilic and lipophilic cargo • Ease of ligand conjugation to improve blood circulation	**Advantages** • Small size • Increased uptake due to ionic interaction with BBB
Limitations • Self-aggregation may impact brain delivery	**Limitations** • Potential cytotoxicity caused by non-specific uptake	**Limitations** • Potential toxicity due to the metal accumulation

Fig. 1 Classes of nanoparticles for brain delivery. Polymeric, lipid, and inorganic nanoparticle delivery systems have been investigated in animal models of SUD. Each nanoparticle class has advantages and limitations related to safety, cargo, and surface modifications.

siRNA [29]. FDA-approved PLGA nanoparticles are also capable of crossing the blood-brain barrier and are remarkably safe as the polymers are broken down to lactic acid and co-glycolic acids—natural metabolites of glycolysis [30]. For brain targeted applications, one preclinical study revealed that PLGA nanoparticles coated with polysorbate 80 and poloxamer 188 significantly improved central nervous system (CNS) delivery [31]. With improved sustained-release properties, PLA and PLA-HPG nanoparticles [32, 33] are being investigated as a potential delivery system for Alzheimer's disease treatments [34, 35]. To improve brain biodistribution, other researchers have found that conjugating trans-activating transcriptor (TAT) peptide to PLA nanoparticles dramatically increased brain uptake in mice [36]. Several other surface modifications to polymeric nanoparticles have also been shown to increase brain delivery of the therapeutic cargo [37–39].

Although polymeric nanoparticles have many positive characteristics for brain delivery, they are not without limitations. For example, the accumulation of polymeric nanoparticles in the liver before the treatment reaches the brain may reduce the therapeutic effect [39, 40]. Uptake by the reticuloendothelial system may also lead to rapid clearance from systemic circulation [40]. Increased clearance and lower distribution may require higher and/or more frequent doses, which may result in unwanted side effects. Nevertheless, polymeric nanoparticles have proven to be versatile in nature, given the ability to encapsulate various types of payloads that can potentially penetrate the blood-brain barrier.

Liposomes

Liposomes are nanovesicles composed of phospholipids that produce a lipid bilayer with a hydrophilic aqueous inner core. Liposomes are able to encapsulate and deliver a variety of therapeutic cargo including hydrophilic and hydrophobic drugs, nucleic acids, peptides, and proteins [41–44] (Fig. 1). The recent success of the Moderna and Pfizer/BioNTech COVID-19 mRNA vaccines, which utilize liposomal delivery systems, has given considerable prominence to this nanoparticle class. Similar liposomal technologies have also been used for brain delivery. For example, nucleic acid-based therapeutics have been delivered to the brain with surface-modified liposomes in animals [45]. In brain delivery experiments, polyethylene-glycol conjugated liposomes were observed to have a greater therapeutic effect than free drug in rats [46]. In clinical studies, Doxil, a liposomal drug

formulation for cancer, has been shown to effectively treat glioblastoma [47], and other liposome-based formulations are being investigated for the treatment of Alzheimer's disease [48]. Although liposomes are versatile in nature, they also carry some downsides in their delivery properties. For example, nonspecific uptake and binding to serum proteins occurs in the bloodstream, requiring high doses to be used for efficacy [49]. Ligand conjugation can increase the binding of liposomes to specific tissues. As example of this approach, Costa and colleagues used liposomes conjugated to chlorotoxin for a more efficient brain targeted therapeutic delivery in mice [50]. Overall, liposomal formulations have strong potential in brain delivery given their ability to mimic membrane properties and cross the blood-brain barrier.

Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are nanocarriers consisting of a lipid core matrix stabilized by an emulsifier, but do not use a bilayer system as in liposomes [51]. SLNs have been favored for drug delivery due to their optimal release profiles and longer shelf life compared to liposome formulations [52]. An attractive characteristic of SLNs is their small size, which may allow them to cross the blood-brain barrier more efficiently than other nanodelivery systems [53]. As SLNs are composed from physiologically similar lipids, they have potentially fewer toxic liabilities [54]. Improved brain targeting with SLNs has been achieved by conjugating ligands to the surface and adding specific coatings to increase brain uptake. For example, coating SLNs with bovine serum albumin was shown to increase transport to the brain in preclinical studies [55]. However, SLNs do have some limitations. Due to their small size, SLNs are subject to rapid release and low loading [56]. Nevertheless, SLNs have the potential to be major aids in brain delivery applications due to their safety profile and controlled release properties.

Gold nanoparticles

Gold nanoparticles have been successfully used for therapeutic brain delivery in preclinical studies [57]. Gold nanoparticles contain an inner inorganic layer surrounded by a nonpolar organic monolayer that stabilizes the inner core and interacts with the environmental targets [58]. This approach enhances solubility and protects the inner core from degradation. The main difference between gold nanoparticles and the previously discussed delivery

Table 1. Nanoparticle-based therapeutics tested in preclinical SUD models.

NP class	Payload delivered	Route of delivery	Therapeutic effect	Reference
Polymeric	Naloxone	Oral	↓ morphine-induced locomotion ↓ precipitated withdrawal	[69]
Polymeric	Naloxone	Subcutaneous	↓ precipitated withdrawal	[70]
Polymeric hybrid	Rifampin Buprenorphine	Oral	↑ removal of morphine from circulation ↓ hepatocellular damage from morphine	[90]
Polymeric	Leucine-enkephalin	Intranasal	↑ antinociceptive response without tolerance	[140]
Polymeric	Leucine-enkephalin	Intranasal	↑ brain delivery ↑ antinociceptive response	[141]
Polymeric	GDNF	Intracranial	↓ cocaine self-administration	[147]
Polymeric	Nicotine vaccine	Subcutaneous	↓ nicotine discrimination	[100]
Lipid-polymeric hybrid	Nicotine vaccine	Subcutaneous	↑ immunogenicity ↓ nicotine levels in brain	[97]
Lipid-polymeric hybrid	Nicotine vaccine	Subcutaneous	↑ anti-nicotine antibody titer ↓ brain nicotine levels	[108]
Lipid-polymeric hybrid	Nicotine vaccine	Subcutaneous	↑ antibody affinity for nicotine ↓ brain nicotine levels	[96]
Lipid-polymeric hybrid	Nicotine vaccine	Subcutaneous	↑ immunological efficacy ↓ brain nicotine levels	[171]
Lipid-polymeric hybrid	Nicotine vaccine	Subcutaneous	↑ anti-nicotine antibody titer ↓ brain nicotine levels	[98]
Lipid-polymeric hybrid	Nicotine vaccine	Subcutaneous	↑ anti-nicotine antibody titer ↓ brain nicotine levels	[99]
Lipid-polymeric hybrid	Cocaine vaccine	Intramuscular	↑ anti-cocaine antibody production ↓ rewarding effects of cocaine	[104]
Lipid-polymeric hybrid	Leucine-enkephalin	Intravenous	↓ rapid plasma degradation of LENK ↑ antihyperalgesic effect > morphine	[142]
Gold	DARPP-32 siRNA	N/A	modulation of dopaminergic signaling pathways in vitro	[117]
Gold	DARPP-32 siRNA	Intracerebral	↓ opioid withdrawal-like symptoms	[118]

systems is that the payload binds to the surface of the gold core instead of encapsulation [59]. Gold nanocarriers are capable of delivering a wide range of therapeutics range from antibiotics to DNA, due to their ability to conjugate to a diverse set of molecules [60, 61]. Like other nanoparticle systems, gold nanoparticles are adaptable to surface modifications allowing for brain and/or cell type-specific targeting [62]. With their small size (<100 nm), gold nanoparticles have been shown to cross the blood-brain barrier in multiple preclinical studies [63, 64]. However, in some experiments, unmodified, highly charged gold nanoparticles have been shown to induce an immune response in the brain, which may limit their therapeutic potential as a SUD treatment [65] (Fig. 1). To address this potential liability, surface modifications that alter the positive charge of the gold nanoparticles have been shown to minimize the potential toxic side effects [66].

NANOPARTICLE-BASED TREATMENTS FOR SUD
Small molecule drugs
Nanoparticles have the potential to bolster the therapeutic efficacy and utility of many FDA-approved small molecule treatments for SUD and SUD-related overdoses (Table 1). For example, naloxone is widely used to reverse opioid-induced respiratory depression, but because of its low oral bioavailability [67], it is typically administered intramuscularly, intranasally, or intravenously. Additionally, naloxone, when acutely administered, has a shorter half-life than many abused opioids, which may lead to renarcotization and a recurrence of opioid-induced respiratory depression [68]. To address these issues, researchers developed polymeric nanoparticles bound to naloxone (NP-naloxone) and demonstrated that this formulation greatly increased the oral bioavailability of naloxone and offered better protection from

opioid overdose in animals by producing a sustained naloxone release [69]. Furthermore, this nanoparticle-based approach has the potential to decrease incidences of opioid antagonist-induced withdrawal, a common drawback of traditional naloxone dosage forms. Unlike some parenteral naloxone formulations, this orally administered NP-naloxone formulation possessed a long duration of action in mice (≥ 24 hours), while maintaining the quick onset of action properties. Consistent with the previous studies, other naloxone-bound nanoparticle formulations were shown to competitively displace morphine from the mu-opioid receptor and selectively block morphine's antinociceptive effects in opiate-dependent mice without causing precipitated opioid withdrawal symptoms [70]. More recently, intranasal delivery of naloxone-loaded lipid nanoparticles was found to be effective at reversing opioid-induced overdose in rats, while also showing greater brain biodistribution compared to naloxone alone [71]. Additional preclinical studies are needed to determine if these nanoparticle formulations are also effective at reversing the actions of other, highly potent opioids (e.g., fentanyl) and whether these naloxone formulations have the potential to reduce drug-seeking and -taking behaviors in animal models of SUD. Furthermore, small molecules that act through non-opioidergic pathways have also been shown to reduced opioid-induced respiratory depression in animals [72], and additional studies are needed to determine if nanoparticle formulations have the potential to improve the pharmacokinetic properties, efficacy, and cell type-specific delivery of these small molecules.

While the previous section focused on nanoformulations for the reversal of opioid-induced respiratory depression, nanoparticle-bound small molecules are also being utilized for long-term SUD treatment. For example, naltrexone is a potent opioid receptor antagonist that attenuates the reinforcing effects of opioids and

4

reduces alcohol craving and intake in humans [73, 74], but because of its poor oral bioavailability and relatively short duration of action, daily oral medication is typically required [75]. As daily medication noncompliance is a major issue associated with naltrexone and other SUD treatments [76], researchers as early as the mid-1970s began to develop sustained release, injectable polymer formulations for opioid receptor antagonists [77–79]. This line of research eventually lead to the FDA-approved, long-acting intramuscular injection form of naltrexone-bound PLGA nanoparticles (Vivitrol®) for the treatment of alcohol and opioid dependence [80–82]. Although Vivitrol® improved noncompliance issues associated with oral naltrexone, patients must return for treatment once a month, which again contributes to high attrition rates [83]. For longer sustained release of naltrexone (>1 month), polymer pellet implants [84–86], microspheres [87, 88], and nanogel [89] formulations are currently undergoing preclinical and/or clinical testing.

In other preclinical studies, Masoumi and Esmaeiiln (2020) developed a nanoparticle formulation containing rifampin and buprenorphine as a potential treatment for opioid dependence. Rifampin is a potent inducer of numerous cytochrome P450 enzymes and will effectively decrease the serum concentrations of many substrates (i.e., opioids), and buprenorphine is a mixed agonist–antagonist opioid receptor modulator that reduces symptoms of opioid withdrawal and craving [90]. However, this approach might be problematic from a clinical prospective, as rifampin has been shown to alter buprenorphine metabolism [91], potentially causing withdrawal symptoms. Other lipid nanoparticles containing buprenorphine have also been investigated in pain studies [92] but have yet to be tested in SUD models. Overall, using nanoparticle formulations to promote the sustained release of small molecule SUD treatments is an effective strategy to increase patient compliance and clinical outcomes. Going forward, researchers are encouraged to investigate the ability of nanoformulations to improve the effectiveness of other small molecules that have shown promise in preclinical and clinical SUD studies.

Vaccines

Vaccines are a promising approach for the treatment of SUD [93]. SUD vaccines work by initiating the production of drug-specific antibodies that rapidly bind to the drug of abuse. This mechanism reduces the ability of the drug to cross the blood-brain barrier and thus attenuates the rewarding effects of the abused substance. In recent years, multiple nicotine vaccines have been tested in clinical trials but have failed to significantly alter smoking cessation [94]. The failure of these conjugate nicotine vaccines is likely due to their suboptimal intrinsic properties, such as insufficient recognition and internalization by immune cells, low bioavailability, and rapid degradation, all of which contribute to poor immunological efficacy [95]. To address these shortcomings, Zhao and colleagues developed a lipid-polymeric nanoparticle-based nicotine vaccine and found that it had improved cellular uptake by dendritic cells and immunogenicity in mice compared to conjugate vaccines [96]. In other preclinical studies, researchers demonstrated that the immunogenicity and pharmacokinetic efficacy of the nicotine nanovaccine, called NanoNicVac, could be improved by modulating the nanoparticle size, hapten density and localization, carrier proteins, adjuvants, and release rate [97–99] (Table 1). With these improvements, NanoNicVac was found to reduce brain levels of nicotine by 71% in mice [99]. Consistent with the previous studies in mice, the nicotine nanoparticle vaccine, SEL-068, effectively reduced the discriminative-stimulus effects of nicotine in nonhuman primates [100]. Importantly, these findings with nicotine have the potential to be applied to nanoparticle-based vaccines for other drugs of abuse.

Immunopharmacotherapy for cocaine use disorder is another emerging area of research [101]. Previous studies have shown that conjugate cocaine vaccines yielded a modest level of anticocaine antibodies and reduced cocaine seeking in multiple animal models [101–103]. However, because cocaine has poor immunogenic properties, improved strategies are needed ensure a robust and sustained anti-cocaine antibody response. By conjugating a cocaine analog to a nanoparticle carrier with major histocompatibility complex (MHC) II-binding moieties, researchers were able to generate a prompt, persistent, and high-affinity anti-cocaine antibody response in animals [104]. Using this nanoparticle approach, brain levels of cocaine were reduced by 80% in mice, and in behavioral studies, conditioned place preference for cocaine was significantly attenuated in nanoparticle-treated mice. Together, these studies demonstrate that nanoparticles significantly improve the effectiveness of SUD vaccines in animal models.

While SUD vaccines have shown promise in animal studies, first-generation vaccines for nicotine and cocaine have failed to demonstrate efficacy in phase III clinical trials [105, 106]. From these initial clinical studies, several ongoing challenges for SUD vaccines have been identified, some of which may be addressed by using nanoparticle delivery systems. For example, in SUD vaccine clinical studies, only a subset of individuals achieved sufficient drug-specific antibody levels [107]. Nanocarrier systems have the potential to alleviate this issue, as nanoparticle-based vaccines exhibited improved immunogenicity and pharmacokinetic efficacy for drugs of abuse and other targets in animals compared to conjugate vaccines [97, 108, 109], but human studies are needed to determine if these effects are translatable. To further improve SUD vaccine efficacy in humans, additional research with conjugate and nanoparticle-based vaccines should focus on understanding the factors that contribute to individual variability in immune response following vaccination (e.g., age, sex genetics, immune system health, history/pattern of drug use, vaccine regimen, antibody selectivity and affinity for the target drug, etc.). This information will help clinicians identify the subset of patients that are most likely benefit from SUD vaccines. Finally, the clinically tested SUD vaccines do not address polysubstance use or the likelihood of a person substituting one drug of abuse for another to circumvent the vaccine. Given the elevated prevalence of polysubstance use [110] and that many drugs of abuse are now laced with synthetic opioids, the development of multivalent vaccines will be essential to improve clinical outcomes. In animal studies, bivalent vaccines that target different opioids have demonstrated effectiveness in initial experiments [111–113], and multivalent nanoparticle vaccines have shown promise in other disease models [114, 115] but have not been tested in SUD-related experiments. Conceivably, the surface geometry of multiple antigen-displaying nanoparticles can be fine-tuned allowing for improved immunogenicity across multiple drugs of abuse. Overall, the clinical data indicates that SUD vaccines may be effective in reducing relapse in the subset of patients that are highly motivated to quit but are less useful in promoting abstinence in active drug users, as these subjects may increase their drug intake to saturate the antibody response [106]. Although nanoparticle delivery systems may improve the immunogenicity and pharmacokinetic efficacy of SUD vaccines, SUD vaccines will likely need to be combined with standard medication-assisted therapy to achieve optimal clinical outcomes.

Nucleic Acids

Remarkable progress has been made in the past few years with FDA approvals of antisense drugs targeting messenger RNA for disease treatment [116]. However, the delivery of nucleic acid-based therapeutics to the brain remains a significant challenge in neuroscience research. In SUD-related preclinical studies, investigators have successfully utilized nanoparticle delivery systems to manipulate addiction-related gene targets (Table 1). For example, using gold nanorod-siRNA complexes, gene expression of dopamine- and cAMP-regulated neuronal phosphoprotein

(DARPP-32), an important target involved in drug-induced neuroplasticity, was effectively silenced in dopaminergic cultured neurons without signs of cytotoxicity [117]. The gold nanorod-siRNA complexes also permeated an in vitro BBB model to a greater degree than free (naked) siRNA. In animal studies, gold nanorod-DARPP-32 siRNA complexes caused sustained knockdown of DARPP-32 and reduced opioid withdrawal symptoms when injected into the periaqueductal gray area [118]. Using gold nanorod-siRNA complexes, long-term gene silencing of DARP-32 (14 days) has also been reported in the rat hippocampus [119]. While more research is needed to explore the potential of nanoparticle-mediated siRNA delivery in addiction models, promising results have been reported in animal models of traumatic brain injury [120], Alzheimer's Disease [121, 122], and Huntington's disease [123] using siRNA-loaded nanoparticles.

Because drugs of abuse alter a multitude of gene networks in the brain's reward system, treatment strategies that have the ability to counteract these numerous adaptations are needed. Emerging evidence indicates that microRNA (miR)-based approaches are ideal for reversing or normalizing the extensive maladaptive neuroplasticity caused by repeated drug use [124]. For example, miR-212 levels are significantly altered in the striatum of rats with a history of cocaine use, and viral-mediated manipulation of this and other miRs in the brain decreased cocaine self-administration [125–127]. In humans, several other miRs are also altered in the brain following chronic drug use [128, 129], an indication that miRs are potentially important targets for clinical intervention.

microRNAs can be manipulated using anti-miRs, a single-stranded oligonucleotide with a complementary sequence to mature miRNA that binds to and inhibits the targeted miR, or by miR mimics that act as a replacement strategy to increase miR functional activity [130]. From a therapeutic standpoint, however, delivery of naked miR mimics or anti-miRs is not a viable option due to their short half-life under physiological conditions and their inability to penetrate the blood-brain barrier [131]. Chemical modifications to anti-miRs, such as locked nucleic acids (LNA) or peptide nucleic acids (PNA) have improved the stability of anti-miRs and miR mimics in vivo applications [132], but even with these modifications, miR-based therapeutics have a limited ability to enter the brain. Encapsulating anti-miRs and miR mimics into nanoparticles is an alternative approach that addresses the shortcomings of miR-based therapeutics. For example, when injected systemically, rabies virus glycoprotein (RVG)-labeled nanoparticles were shown to effectively delivery miR-124a oligomers to the mouse brain [133]. Using Neuromag® anti-miR-134 nanocomplex, expression of miR-134 was reduced by 50% in the rat striatum 7 days post-intracerebroventricular injection [134]. Although these initial proof of concept studies are encouraging, nanoparticle-mediated brain delivery of anti-miRs and miR mimics has been primarily confined to brain cancer [135–137] and stroke studies [138]. Going forward, researchers are encouraged to test the effectiveness of nanoparticle-mediated delivery of siRNAs and microRNAs in sophisticated SUD models.

Peptides and Proteins
With low metabolic stability and a diminished ability to cross the blood-brain barrier, peptide and protein-based therapeutics for SUD have had limited clinical applications. In preclinical studies, nanoparticle delivery systems have been shown to address some of these pharmacokinetic liabilities (Table 1). For example, the endogenous opioid peptide leucine-enkephalin (LENK) plays an important role in SUD and pain processing but has a short half-life under physiological conditions [139]. By encapsulating LENK in nanoparticles, Godfrey and colleagues demonstrated that LENK entered the brain to a greater degree than the free form of LENK and produced tolerance-free analgesia in multiple pain assays [140]. Other studies have also shown that LENK-loaded

nanoparticles increased brain uptake and antinociceptive effects following intranasal and systemic administration [141, 142]. Improved brain delivery of oxytocin and substance P have also been achieved following nanoparticle encapsulation, but these formulations have yet to be tested in SUD models [143, 144].

Similar to peptides, proteins, such as, brain-derived neurotropic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) are potential therapeutic agents for the treatment for SUD [145]. By binding to magnetic nanoparticles, BDNF was shown to cross an in vitro model of the blood-brain barrier to a greater degree than free BDNF and increase dendritic spine density [146]. In other studies, GDNF-conjugated nanoparticles, when injected into the rat striatum, reduced acquisition of cocaine self-administration, but did not alter other behaviors, such as water self-administration [147]. Taken together, these findings indicate that nanoparticles represent a safe and feasible strategy for more efficient brain delivery of peptides and proteins.

Gene editing technologies
With the development of CRISPR-Cas9 systems, there has been a growing interest in using gene-editing techniques to study the underlying mechanisms of SUD. However, due to the large size of Cas9 ribonucleoprotein and the low stability of single guide RNAs (sgRNA), protecting these molecules from degradation during delivery has been a challenge [148]. Although truncated Cas9 ribonucleoproteins have been developed (e.g., *Staphylococcus aureus* Cas9, saCas9) [149], packaging the genetic material of Cas9, sgRNAs, and reporters into a single virus remains problematic [150]. Furthermore, viral-mediated constitutive expression of saCas9 and sgRNA in neuronal cells may result in unintended consequences [151]. To address these issues, researchers recently demonstrated that CRISPR-Gold (Cas9 packaged into gold nanoparticles) was able to safely edit genes in neurons, astrocytes, and microglia when injected into the mouse brain [152]. In the same report, CRISPR-Gold was successfully used to edit the metabotropic glutamate receptor 5 (mGluR5) gene in the mouse striatum and improve behavioral symptoms in a mouse model of amyotrophic lateral sclerosis. Tissue-specific gene editing has also been demonstrated following systemic administration of nanoparticle-encapsulated CRISPR-Cas9 [153], but further work is needed to determine if these Cas9- and sgRNA-bound nanoparticles are also able to cross the blood-brain barrier. From a therapeutic standpoint, modulation of gene expression levels, rather than gene knockout, is likely a more attractive treatment approach for SUD. In a technique called CRISPR activation and interference (CRISPRa and CRISPRi), a catalytically inactive Cas9 is fused to a transcription activator or repressor domain, and when combined with sgRNAs, this method allows for gene-specific activation or repression [154]. Though viral-mediated expression of CRISPRa/i has been demonstrated in the brain following an intracranial injection [155, 156], future studies are needed to determine if nanoparticle-mediated delivery of CRISPRa/i into the brain is an achievable approach in animal models of SUD.

OUTLOOK OF NANOPARTICLE-BASED TREATMENTS FOR SUD
With the use of nanotechnology, brain delivery of many small molecules, biologics, and nucleic acids-based treatments is now possible. By encapsulating poorly water-soluble drugs and protecting nucleic acids and proteins from enzymatic degradation, nanoparticles ensure that the payload enters the brain and remains functional upon delivery. With surface modifications, nanocarriers can reduce the toxicity of treatments by targeting disease-associated brain cells while reducing exposure to healthy tissues [157]. The controlled release kinetics of nanoparticles formulations, combined with their capacity to delivery diverse therapeutics, may also reduce the total number of doses needed, potentially improving patient compliance and clinical outcomes.

Despite these benefits, few SUD researchers have tested nanocarrier systems in sophisticated preclinical animal models of SUD. Access to nanoparticle formulations is likely one factor that has restricted such studies. While viral vector core facilities and vendors are widely available and utilized by neuroscience and SUD researchers, nanoparticle core facilities are less abundant. As a result, SUD researchers may not fully appreciate the capabilities of nanocarrier systems as an alternative approach to viral vectors. Thus, further collaborations between nanomedicine and SUD investigators are necessary to unlock the therapeutic potential of nanoparticle products for SUD.

Although a tremendous number of advancements in nanocarrier systems have been made in recent years, many unanswered questions remain regarding their potential clinical utility for SUD. For example, what class of nanoparticles is the best for brain delivery in SUD models? To date, most SUD-related studies administered nanoparticles directly into the brain or tested the nanoparticles in an in vitro blood-brain barrier model, which limits our understanding of its translatable potential. In other brain disease models, multiple classes of nanoparticles have been found to enter the brain following a systemic injection [158–161]. However, to our knowledge, there have been few head-to-head comparisons of brain delivery between the different classes and/ or formulations of nanoparticles. Secondly, what is the best route of delivery? In preclinical studies, intranasal delivery of drug-bound nanoparticles showed superior pharmacokinetic qualities and CNS bioavailability when directly compared to intravenous delivery [162]. Thus, nose-to-brain delivery of nanoparticles may be a preferred approach for future SUD-related studies.

Finally, what surface modifications are likely to increase brain uptake and/or cell type-specific delivery? Thus far, the majority of studies have focused on disrupting the blood-brain barrier to improve nanotherapeutic delivery. For example, as a strategy to reduce brain efflux of therapeutic agents, Gomes and colleagues demonstrated that nanoparticles containing siRNAs for P-glycoprotein (P-gp) efflux transporters increased drug permeability of an in vitro blood-brain barrier model [163]. In preclinical studies, other researchers have utilized ultrasound to disrupt the blood-brain barrier, allowing brain region-specific uptake of nanoparticle-bound treatments [164, 165]. Nanoparticles containing ligands (e.g., transferrin, insulin, leptin, low-density lipoprotein) that bind to receptors on the circulation side of the blood-brain barrier is another approach that has been shown to facilitate transport across the blood-brain barrier via receptor-mediated transcytosis [166]. For cell-type-specific targeting, Tat and RVG-bound nanoparticles have been shown to facilitate uptake in neurons, while quantum dot formulations have been found to selectively target microglia in preclinical experiments [167–169]. Last, drug-induced changes in the brain's microenvironment is an important factor to consider when designing nanoparticles for SUD treatment. For example, blood-brain barrier permeability and integrity may differ depending on the drug(s) abused and the duration of drug use [170], generating additional opportunities or barriers for nanomedicine products.

To move the field forward, more testing and validation is needed using clinically relevant routes of administration (e.g., intravenous, intramuscular, intranasal, intrathecal) in sophisticated SUD models (e.g., operant self-administration, reinstatement, behavioral economic procedures). Additionally, SUD researchers should determine what surface modifications to nanoparticles may increase cell type and/or tissue-specific uptake. Such an approach has the potential to limit side effects following systemic administration. As sustained release nanoformulations are a proven strategy to increase compliance and efficacy in SUD patients, researchers should also identify other small molecules-based therapies that may benefit from nanoparticle delivery systems. Finally, SUD researchers are encouraged to closely examine what nanoparticle delivery strategies have had success in other neurological models and investigate whether similar formulations have potential usefulness in SUD. Continued efforts to address these questions may reveal promising nanotherapeutic avenues for SUD.

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