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Nano-Assisted Drug Delivery Systems for the Improved Treatment of Neuropsychiatric Disorders

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WHAT IS ALREADY KNOWN ON THIS TOPIC?

- *We already knew that nanotechnology is a promising field with significant potential in bypassing the blood–CNS barriers.*
- *However, a little information is currently available to address the efficacy of nanotechnology in treating neuropsychiatric disorders.*

WHAT THIS STUDY ADDS ON THIS TOPIC?

- *This review first focuses on the role of the NPs in drug delivery to neuropsychiatric disorders, and second synthesizes the latest literature to strengthen the foundation of knowledge.*

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ABSTRACT

Psychiatric disorders are among the top causes of disability and morbidity worldwide. Despite the rapid progression of psychiatric pharmaceuticals, there are still significant challenges for the effective management of psychiatric disorders. The blood–brain barrier significantly restricts the access of psychiatric drugs to target cells in the brain tissues. The use of drug-loaded nanoparticles (NPs) is now well considered a viable option for improving the treatment efficacy of currently available drugs and reducing adverse effects. This review summarizes the recent advances and provides the unique characteristics of NP-based formulations as a promising avenue for targeted drug delivery for psychiatric disorders.

Keywords: Depression, drug delivery, nanoparticle, psychiatric disorders, schizophrenia

INTRODUCTION

Psychiatric disorders are defined as conditions with a clinically significant disturbance in thinking, cognition, emotion, or behavior that may not be readily controlled by the individual. Bipolar disorder, depression, anxiety disorders, schizophrenia, and other psychotic disorders are identified as mental illnesses that have adverse consequences not only on individual global functioning but the burden of disease as well. Despite significant progress in the development of effective treatment strategies for psychiatric disorders, efficient drug delivery to the central nervous system (CNS) is still a significant challenge today. The blood–brain barrier (BBB), while protecting the brain from harmful substances, may restrict the access of drugs to the CNS.[1] A combination of existing psychiatric medications with nanoparticles (NPs) can be a solution to address this challenge.

Nanopsychiatry was first introduced by Fond and collaborators, highlighting the potential role of nanotechnology in designing drugs, treatments, and diagnostic tools for mental illnesses.[2] Specifically, nanotechnology offers multiple benefits as pharmaceutical systems in delivering drugs, lipids, proteins, and/or genetic materials. Nanoparticles are materials with sizes ranging from 1 to 100 nm that exhibit excellent features compared to their counterparts at larger sizes. Due to their unique physical

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- *This paper details the synthesis method and cell-type-specific actions of NPs in the CNS and discusses the need to use natural resources for the synthesis of new nanoformulations with therapeutic efficiency.*
- *Specific information can be found in this review on how researchers can design and develop safe and efficient nanoformulations for the management of neuropsychiatric disorders.*

properties, NPs are thought to have improved reactivity, reduced thermal resistivity, and successful intracellular delivery of therapeutics. Nanoparticles exhibit a large surface-to-volume ratio that acts as reservoirs or carriers, making them ideal for drug delivery. Recently, several studies have focused on investigating the efficacy of nanosystems to encapsulate antipsychotics for targeted drug delivery to the brain, thereby increasing their bioavailability. In this review, we discuss the use of nano-based drug delivery systems for the treatment of psychiatric illnesses.

NANOPARTICLES FOR DRUG DELIVERY IN PSYCHIATRIC DISORDERS

One of the most significant barriers in the CNS is the BBB that complicates the concentration and entry of therapeutic drugs. To overcome this obstacle, drugs can be loaded inside NPs that are characterized by their ultra-small size and ability to penetrate the BBB. Moreover, NPs can assist treatments by protecting drugs from digestive enzymes, improving their pharmacokinetics, and allowing a sustained release of the drug within the body. Nanoparticles used for brain drug delivery can be divided into different categories according to their composition, namely polymer-, lipid-, surfactant-, metal-, and carbon-based NPs.

Overall, NPs made up of biodegradable materials are especially attractive because of their low toxicity. NPs can be engineered to have specific surface properties that allow them to promote the efficacy of psychotropic drugs by improving low bioavailability, plasma half-life, and water solubility. Modification with polyethylene glycol (PEG) is a common strategy to improve NPs circulation time and reduce mononuclear phagocyte system clearance. The mechanisms of NPs transportation through the healthy BBB can be classified into several main types including paracellular pathway, transcellular pathway, receptor-mediated transport, carrier-mediated transcytosis, and adsorptive transcytosis (Figure 1).[3]

More importantly, BBB disruption in different psychiatric conditions can be considered an opportunity to design more efficient NPs for brain delivery. The nasal route has attracted significant attention in nanopsychiatry as it is a direct, non-invasive way to transport NPs for delivering drugs directly to the brain. During the last decades, the efficiency of NPs in helping reduce the symptoms of psychiatric conditions has been extensively been examined. In light of these findings, we highlight the advantages and disadvantages of different NPs in treating psychiatric disorders. Of note, several scientific publications about using NPs in treating psychiatric disorders are also shown in Table 1.

Polymer-Based Nanoparticles

In recent years, several studies have been conducted to associate psychiatric drugs with polymeric NPs. Various natural (e.g., gelatin, chitosan, and alginate) and synthetic polymers (e.g., poly [D-lactic-co-glycolic acid) [PLGA], polylactic acid [PLA], polycaprolactone, poly(alkylcyanoacrylate) [PACA], and

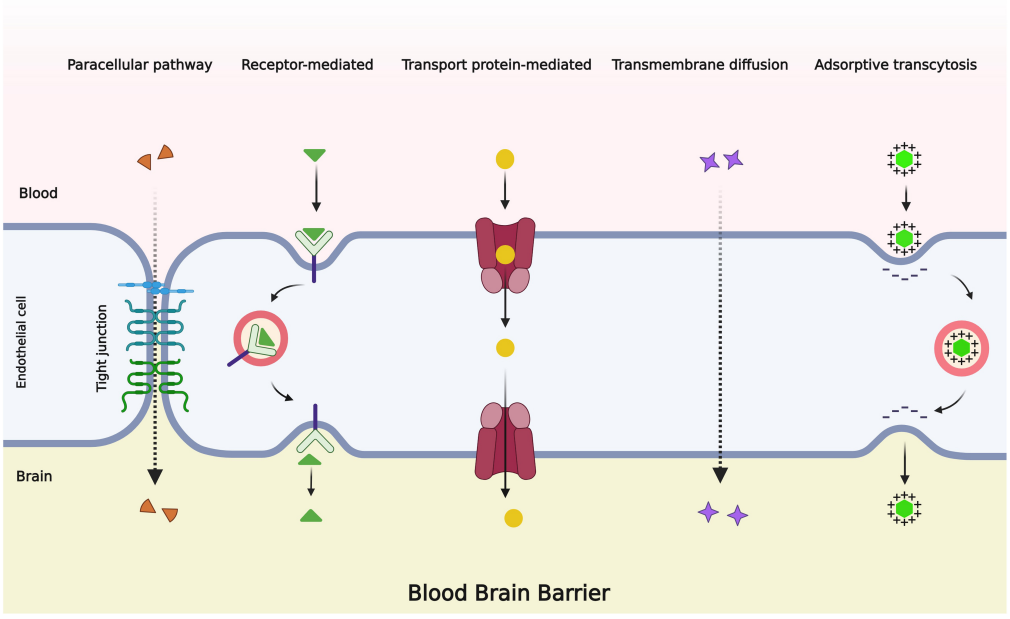

Figure 1. The main mechanisms of NP-mediated drug transport across the BBB.

Table 1. Application of NPs for Drug Delivery and Treatment of Psychiatric Disorders

Nano Carrier/ Components	Drug	Mental Illness	Route of Administration	Method of Preparation	Characterization	%DTE/%DTP	Ex Vivo/In Vivo Studies	Toxicity	References
PLGA-chitosan NPs	Desvenlafaxine	Depression	IN	Solvent emulsion evaporation	PS: ~172 nm ZP: +35 mV	–	Rodent depression models	–	4
Chitosan NPs coated with polysorbate 80	Thymoquinone	Depression	IP	Ionic gelation	PS: 492.3 ± 141.25 nm PDI: 0.453 ZP: 3.89 ± 2.23 mV EE: 85.61% ± 1.02	–	Wistar rodents	–	5
NPs and hydrogel/ starch NPs and mucoadhesive chitosan oligosaccharide lactate	Olanzapine	Schizophrenia	IN	In situ-gelling	PS: 10-20 nm	–	Male Sprague–Dawley rats	Non-toxic	6
Nanofiber/ polyethylene oxide (PEO), l xylitol or Kollidon VA64	Risperidone	Psychotic disorders	Oral	Electrospinning	PS: 450 and 1100 nm	–		–	7
Micelle/amphiphilic copolymers of Pluronic® F127 and Gelucire® 44/14	Lurasidone	Schizophrenia and bipolar depression	IN	Solvent evaporation method	PS: 175 nm EE: 98%	394% and 74%	Wistar rats and sheep nasal mucosa	Non-toxic	8
Micelle/Pluronic 123/ F127	Olanzapine	Schizophrenia	IN	Thin film hydration	PS: 37.5-47.55 nm	–	Male Wistar rats	Non-toxic	9
Micelle/D-alpha-tocopheryl polyethylene glycol 1000 succinate (Vitamin E TPGS)	Paliperidonepalmitate	Psychotic/schizophrenic disorders	–	Solvent casting method	PS: 26.5 nm EE: 92.61 ± 2.5	–	In vivo Swiss albino mice (apomorphine-induced)/ intramuscular	–	10
Micelle/Pluronic F127	Aripiprazole	Psychotic/schizophrenic disorders	–	Thin film hydration	PS: 170.3 nm PDI: 0.228 ZP: −4.04 mV EE: 76.50%	–	–	–	11
Liposome	Risperidone	Schizophrenia	IN	Thin film hydration	PS: 90-100 nm PDI: 0 < 0.5 EE: 50%-60%	–	Wistar rats	–	12
Liposome	Quetiapine fumarate	Schizophrenia	IN	Thin film hydration	PS: 139.6 nm ZP: −32.1 mV EE: 78.66 ± 3.42	–	Albino mice	Non-toxic	13
Nanoemulsion/ Capmul MCM, Tween 80	Quetiapine fumarate	Schizophrenia	IN	High-sheer ultrasonication	PS: 144 ± 0.5 nm ZP: −8.131 ± 1.8 mV Drug content (%): 91 ± 0.3	267.98% ± 3 and 63.63%	Male Wistar rats	–	14
NPs/Fe_2O_3, 3-aminopropyltriethoxysilanen	Peptide antisauvagine-30 (ASV-30)	Psychotic/ schizophrenic disorders	–	Refluxing	PS: ~5 ± 1 nm	–	Male Sprague–Dawley rats	–	15

DTE, drug targeting efficiency; DTP, direct transport percentage; EE, entrapment efficiency; IN, intranasal; IP, intraperitoneal; PDI, poly dispersity index; PS, particle size; ZP, zeta potential.

poly-lysine) are utilized for the fabrication of polymeric NPs. Polymers can be applied in the development of different nanostructures such as NPs, micelles, dendrimers, and nanogels. Polymer-based NPs can easily carry different therapeutic agents like a drug, gene, protein, or vaccine. Therapeutic agents can not only be entrapped in the core of polymeric NPs but also be bound or adsorbed on their surface. Polymer-based NPs have good colloidal stability and sustained release, enhancing the absorption of loaded cargo.

Nanoparticles: Polymeric NPs possess multiple advantages rendering them ideal candidates for drug delivery in psychiatric disorders such as high loading capacity, thermodynamic stability in biological media, and controlled release properties. In 2007, Budhian et al[16] successfully synthesized haloperidol-loaded PLA and PLGA NPs using homogenization and sonication techniques. In another report, a thermal-responsive in situ gel containing risperidone-loaded PLGA NPs was fabricated by the nanoprecipitation method using Poloxamer 407 as a polymeric stabilizer. Through in vivo studies in mice, the prepared formulation showed a prolonged antipsychotic effect for up to 72 hours compared to risperidone solution. These results highlighted the effectiveness of PLGA NPs to penetrate the BBB with fewer extrapyramidal side effects.[17] In recent years, green synthesis has been shown as a more advanced method of NPs production over traditional methods because of its simplicity, nontoxicity, and efficiency. The green synthesis technique uses living organisms like yeast, bacteria, fungi, or plants instead of harmful chemicals to reduce metal ions. Lopez-Maldonado et al[18] developed 3 new green olanzapine nanocomposites using chitosan as the base biopolymer and tripropylphosphate (TPP) and alginate as cross-linking agents with potential application in nanopsychiatry. Chitosan-based complexes showed good physicochemical characteristics (particle size, zeta potential, etc.), allowing a high encapsulation efficiency of olanzapine at pH 5.0. These findings demonstrated that TPP and alginate have a critical role in the green synthesis of olanzapine nanocomposites. Valproic acid is primarily used in the treatment of bipolar disorder. However, the toxic metabolites of valproic acid interfere with its therapeutic use. It was found that dextran and Tween-coated NPs may help to reduce the toxic effects of valproate by inhibiting the metabolic degradation of valproic acid via mitochondrial β-oxidation and reducing the therapeutically necessary dosage.[19]

Micelles: Polymeric micelles represent a significant advancement in drug delivery systems, particularly for administering hydrophobic therapeutic agents through systemic routes. These nanostructures, typically less than 100 nm in diameter, form spontaneously in solution through a self-assembly process. The architecture of polymeric micelles is characterized by a unique spheroidal configuration. At their core lies a hydrophobic region, which is enveloped by a protective outer layer composed of hydrophilic molecules. This dual-nature structure confers several advantages to the micelle as a drug carrier.[20] The hydrophilic exterior serves a crucial protective function. By shielding the micelle from immediate recognition by the reticuloendothelial system, it enhances the stability and longevity of the structure within biological environments. This feature allows for prolonged circulation times and improved drug efficacy.[21] Conversely, the hydrophobic interior of the micelle acts as a reservoir for water-insoluble therapeutic agents. These drugs can be incorporated into the core through physical entrapment or chemical conjugation, providing flexibility in drug loading methods. These characteristics make polymeric micelles a promising tool in the ongoing quest for more effective and tailored drug delivery systems in psychiatric disorders. Research by Piazzini and colleagues[22] explored the use of micelles loaded with aripiprazole, an antipsychotic drug. Their study assessed improvements in permeability, dissolution, and bioavailability both in laboratory settings and living subjects, focusing on schizophrenia management. Singla et al[23] investigated the sustained-release properties of hydrophobic drugs, specifically clozapine and oxcarbazepine, when solubilized in Pluronic mixed micelles of varying molecular weights. Their findings, based on both in vitro and in vivo experiments, suggest that this approach could be particularly beneficial for drugs with poor solubility and limited ability to cross the BBB. A novel nose-to-brain drug delivery system was developed using mixed micelles of Tat-conjugated and bombesin-modified polymers. This system showed improved tumor selectivity and efficacy compared to the previous Tat-only micelles when delivering camptothecin to glioma cells and rat brain tumors. The mixed micelles demonstrated enhanced cellular uptake, cytotoxicity, and tumor-specific accumulation, resulting in prolonged survival in a rat glioma model.[24]

Dendrimer: Dendrimers are sophisticated nanostructures with unique properties that make them promising candidates for drug delivery systems, particularly in targeting the CNS. These highly ordered, branched molecules possess a distinctive architecture comprising a central core surrounded by inner and outer shells. Their nanoscale size and branched structure can be precisely engineered, offering tailored solutions for drug delivery.[25] A key advantage of dendrimers is their ability to form spherical structures with internal cavities capable of encapsulating drug molecules. This feature, combined with the option to modify their surface with biocompatible compounds, enhances their pharmaceutical potential. Such modifications can reduce toxicity and immunogenicity while improving tissue permeability and enabling targeted drug delivery. A significant application of dendrimers in antipsychotic drug delivery is illustrated by the work of Katare et al[26] on haloperidol, an antipsychotic medication with poor water solubility. They developed haloperidol dendrimers (15.10 nm, 10.7 mV zeta potential) with 100-fold higher aqueous solubility and improved brain biodistribution. The intranasal administration of these dendrimers showed comparable efficacy to 6.7 times larger intraperitoneal doses of haloperidol solution. One of the most striking outcomes was the substantial improvement in haloperidol's aqueous solubility—the dendrimer formulation increased it by more than 100-fold. This dramatic enhancement in solubility directly contributes to improved absorption and distribution of the drug within the CNS. However, it is crucial to acknowledge the challenges in the widespread clinical application of dendrimers. The complex synthesis process required for many dendrimers presents difficulties in scaling up production for clinical trials, potentially limiting the assessment of their efficacy on a larger scale.[27]

Nanogel: Nanogels represent an innovative therapeutic approach in drug delivery for various neurological and psychiatric conditions, including schizophrenia, migraine, and depression. These hydrogel-based nanostructures offer a promising method for administering medications, particularly via the intranasal route, which allows for effective management of CNS disorders through the olfactory nerve pathway. A key feature of nanogels is their cross-linked polymer network, which contributes to their unique properties.[28] The polymer component of nanogels can swell, enhancing drug-loading capacity. Meanwhile, cross-linking provides structural stability. This

combination of features allows nanogels to penetrate the BBB and release their payload at specific target sites within the CNS. In a notable study, Stoilova et al[29] developed novel nanogels using N, N-dimethylacrylamide and β-cyclodextrin triacrylate to enhance the solubility and therapeutic efficacy of aripiprazole. Another study explores a novel approach using neural cell membrane coatings on DNA nanogels to enhance delivery specificity. The researchers created nanogels coated with membranes from four CNS cell types, demonstrating improved cellular uptake compared to uncoated nanogels. Notably, oligodendrocyte progenitor cell membrane-coated nanogels showed selective uptake by oligodendrocytes both in vitro and in vivo, as well as effective gene knockdown capabilities. This innovative technique leverages natural cell-cell interactions to improve targeted drug delivery, potentially advancing treatments for CNS injuries and disorders.[30]

Lipid-based Nanoparticles

Lipidic NPs can be categorized into several subgroups, including liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid nanoemulsions.

Liposomes: Liposomes are now the most often used lipid-based NPs due to their excellent biocompatibility, flexibility, and ability to encapsulate a wide range of drugs. Structurally, liposomes are nano-sized spherical vesicles consisting of 1 or more phospholipid bilayers surrounding an aqueous core. This structure gives liposomes the important advantage of being capable of encapsulating both hydrophilic and hydrophobic molecules. Liposomes are more lipophilic and therefore have a strong BBB penetration ability, resulting in a higher concentration of the drug in brain tissue. A single administration of amphotericin B liposomal to mice was reported to have therapeutic and prophylactic effects on the chronic social defeat stress-triggered behavioral abnormalities by stimulating innate immune cells.[31] Accumulating evidence suggests that neuroinflammation plays an important role in pathophysiology and the treatment of depression. Zhou et al[32] established oxytocin-loaded liposomes, and N-Acetyl Pro–Gly–Pro (PGP) was used as a targeting ligand for liposomes. The PGP peptide shows high specific binding affinity to the CXCR2 receptor of neutrophils. According to the results, inflammation-induced BBB disruption and neutrophil infiltration provide an effective way to enhance oxytocin liposomes, especially in the amygdala, after intravenous injection, ameliorating depressive-like behaviors (Figure 2). It is noteworthy to say that low stability and leakage of payload from the vesicles remain major challenges in designing liposome-based drug delivery systems. To address these issues, a number of lipid-based NPs with improved characteristics, like SLNs and NLCs, have initiated a new area of research in nanopsychiatry.

Solid Lipid Nanoparticles: Solid lipid nanoparticles are characterized by the presence of a solid lipid core matrix such as triglycerides, fatty acids, or waxes stabilized by surfactants (emulsifiers). Solid lipid nanoparticles are frequently suggested as a novel nontoxic formulation to carry drugs across the BBB. Thymoquinone SLNs have been shown to exert good antidepressant-like activity and reduce symptoms of depression in a chronic forced-swim stress rat model.[5] Solid lipid nanoparticles have been exploited as a probable carrier to enhance brain bioavailability of olanzapine with less dose administration. Pharmacokinetics assessments in conscious male Wistar rats indicated that olanzapine-SLNs resulted in a 23-fold increase in drug bioavailability in the brain after intravenous administration, reducing extrapyramidal symptoms.[33] In another study, Farsani et al[34] suggested SLNs as a promising perphenazine vehicle for the treatment of schizophrenia.

Nanostructured Lipid Carriers: Nanostructured lipid carriers are nano-sized colloidal drug delivery systems composed of a matrix combining both solid and liquid lipids. Maqsood et al[35] used NLCs for the effective brain delivery of levosulpiride, which has anti-psychotic and antidepressant effects. The in vivo experiment in lipopolysaccharide-induced mice demonstrated that levosulpiride-NLCs could reduce the brain levels of neuro-inflammatory markers (p-NF-κB and COX-2). More importantly, no neuro-degeneration and neuro-inflammation were detected in the brains of mice group treated with levosulpiride-NLCs. In another study, NLCs were capable of improving drug stability, bioavailability, and site-specific brain targeting following intranasal administration aimed to treat schizophrenia.[36] Clozapine-loaded NLCs have been shown to be a potential formulation for increasing clozapine solubility and extending its release.[37]

Nanoemulsion: Emulsions are dispersed systems composed of 2 immiscible liquid phases, typically created through mechanical shear and stabilized by surfactants. These formulations offer several advantages in drug delivery, particularly for hydrophobic or oil-soluble medications**.** A key benefit of emulsions, especially relevant to antipsychotic medications, is their ability to improve the bioavailability of lipophilic drugs. Aripiprazole, a third-generation antipsychotic, exemplifies the potential of emulsion-based formulations. Recognized for its efficacy in managing schizophrenia symptoms, aripiprazole was the first atypical antipsychotic to receive approval from the U.S. Food and Drug Administration.[38] Recent research has explored the development of nanoemulsions containing aripiprazole, utilizing high shear and high-pressure homogenization techniques. The study examined the influences of palm kernel oil ester, lecithin, Tween 80, glycerol, and water on the size of aripiprazole nanoemulsion droplets. The droplet size was 62.23 nm. The small droplet size not only enhances encapsulation efficiency but also potentially improves the drug's bioavailability and targeted delivery within the body.[39]

Surfactant-Based Nanoparticles

Surfactant-based NPs can be prepared from the self-assembly of surfactants, a unique class of surface-active molecules, in aqueous media assisted by agitation or sonication.

Niosomes: Niosomes are self-assembled vesicular nanocarriers made up of non-ionic surfactants with or without cholesterol. Niosomes have already been reported to increase the brain bioavailability of psychoactive drugs. Gangane et al[40] developed an intranasal thermosensitive gel containing venlafaxine niosomes for the effective management of chronic depressive disorder. The in vivo pharmacokinetic study in rats demonstrated a higher concentration of venlafaxine in the brain and plasma. The aim of a recent study was to evaluate an in-situ gel containing amisulpride-loaded niosomes to improve nose-to-brain delivery. This study demonstrated that niosomal nanoformulation could improve amisulpride permeation via the nasal route and enhance plasma and brain concentrations, resulting in improved anti-schizophrenia effects.[41] Khallaf et al[42] indicated that chitosan-coated niosomes led to higher permeation of olanzapine across the nasal mucosa than the uncoated ones and plain drug solution likely due to the presence of a non-ionic surfactant in the vesicles' structure, known as a permeation enhancer. Moreover, it should also be considered that chitosan can also be

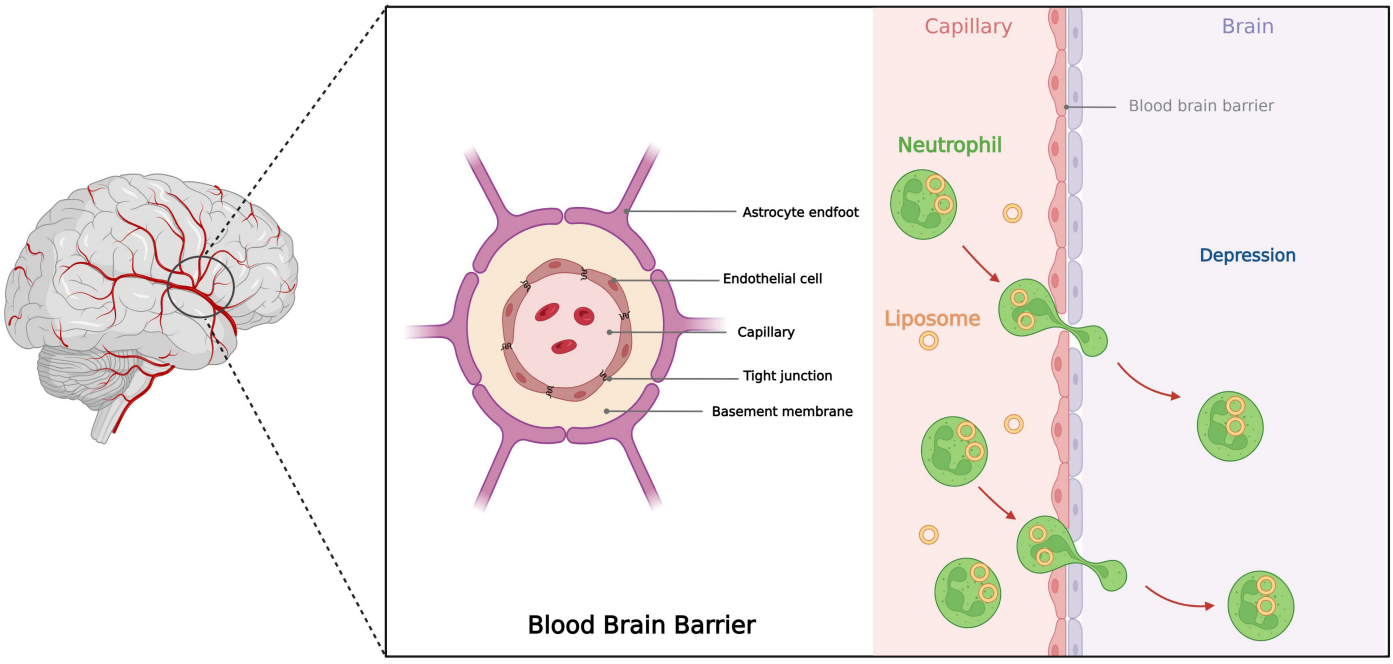

Figure 2. Cell-liposome delivery system based on neuroinflammation for ameliorating depressive-like behaviors.

considered a permeation enhancer due to its mucoadhesive properties and ability to transiently open the epithelial tight junctions.

Inorganic Nanoparticles

Inorganic NPs include materials such as silica NPs and metal NPs. These particles display a wealth of structural and optical properties, offering a promising platform for neuroimaging and brain drug delivery.

Silica Nanoparticles: Among the different types of inorganic NPs, silica NPs are the most produced engineered nanomaterials. Silica NPs can be classified into two main groups: mesoporous silica NPs and nonporous (solid) silica NPs. Silica NPs are particularly promising in nanopsychiatry applications due to their tunable particle size and porosity, large specific surface area, good biodegradability, and biocompatibility.[43] In this regard, Fahmy et al[44] successfully developed Gallic acid-loaded mesoporous silica NPs with a diameter of 241.6 nm and zeta potential of −31.4 mV as effective nanoplatforms for delivering medications to the brain. The antidepressant efficacy of Gallic acid was enhanced by its loading to mesoporous silica NPs. Gallic acid-loaded mesoporous silica NPs could reduce oxidative stress and elevate monoamine levels in a reserpine-induced depression model in rats.

Metal Nanoparticles: Currently, metal NPs have received much attention in brain delivery for effective and accurate imaging and management of psychiatric disorders. Some of the commonly synthesized metallic NPs are gold (Au), silver (Ag), iron (Fe), copper (Cu), cadmium (Cd), zinc (Zn), and palladium (Pd). Metal NPs are used in neuroimaging and can be modified to cross the BBB. Surface coatings like PEG or lactoferrin improve their stability and BBB penetration. Some, like iron oxide NPs (IONPs), can be manipulated with magnetic fields for targeted delivery. Saeidienik et al[45] investigated potential effect of IONP administration in attenuating depression symptoms. This effect is possibly mediated by the modulation of neurotransmitters and the anti-inflammatory effects of iron NPs. The antidepressant efficacy of green synthesized curcumin-IONPs was reported in a recent study conducted by Khadrawy et al[46] The in vivo experiment in depressed rats indicated that treatment with curcumin-IONPs for 2 weeks increases serotonin, norepinephrine, and dopamine levels. Curcumin used in the IONP synthesis attenuates oxidative stress induced by iron. Meanwhile, it opens a potential treatment avenue for cognitive enhancement in neurodegenerative disorders, including Alzheimer's disease, through increased Klotho levels as an anti-aging protein expression in CNS.[47] These inorganic NPs, and their combinations with natural materials, exhibit unique physical, chemical, optical, and electrical properties that set them apart from other nanoscale materials. However, their non-biodegradability raises toxicity concerns, necessitating further research. In the context of antipsychotic medications, AuNPs have shown potential for enhancing drug efficacy and delivery. One notable example is the use of AuNPs in conjunction with thioridazine, a phenothiazine-class antipsychotic sometimes used in schizophrenia treatment.[2] The enhanced encapsulation efficiency offered by AuNPs could lead to improved bioavailability of antipsychotic drugs. However, it is crucial to note that the use of AuNPs in drug delivery systems is not without challenges. While the surface modification of AuNPs can mitigate some toxicity concerns, the toxicokinetic profile of these NPs remains a critical consideration. As research in this field progresses, it will be essential to balance the promising benefits of AuNP-based drug delivery systems with a comprehensive understanding of their safety profile. This approach could potentially revolutionize the treatment of schizophrenia and other neuropsychiatric disorders by offering more targeted and efficient drug delivery methods.

Carbon-based Nanoparticles

Carbon-based NPs have the potential to improve treatment techniques for neuropsychiatric disorders. They are commonly classified according to their structure into fullerene, carbon dot, carbon nanotube (CNT) (single-walled carbon nanotube [SWCNT] and multi-walled carbon nanotube [MWCNT]), and nanodiamonds. Carbon nanotubes are being researched for biomedical uses, particularly

in neurological conditions, due to their electrochemical properties. A recent study investigated the effects of NPs-graphene oxide (GO), multilayer carbon tubes (MWCNTs + Fe), magnetite (Fe_3O_4), and in situ forming brushite (DCPD) on chitosan-based nerve conduits (NCs). The research examined cytotoxicity, drug release kinetics, and in vivo performance. NP concentrations ≤150 µg/mL were non-toxic, while 300 µg/mL Fe_3O_4 promoted apoptosis in nerve cells. Pregabalin release kinetics were optimized when introduced during DCPD formation. Graphene oxide- and MWCNTs + Fe-containing NCs demonstrated ~6-month biodegradation periods.[48] Another study examined the distribution and effects of 2 intranasally delivered MWCNTs in rat brains, focusing on their potential neuroprotective properties in early diabetic encephalopathy. The research found that both CNT types reached various brain regions, especially limbic areas crucial in neurodegenerative diseases. Notably, the electroconductive MWCNTs showed neuroprotective effects by modulating a key neurotrophic factor and potentially improving neurodegenerati on-related gliosis.[49]

CONCLUSION

Nanotechnology provides a promising platform for improving psychiatric treatments. Many nanoformulations of psychiatric agents are already under laboratory research practice. Using NPs as a delivery mechanism significantly increases drug bioavailability and reduces side effects. Targeted delivery by NPs positively impacts on the biodistribution of psychiatric drugs as well as their efficacy. Nanoparticles synthesized from naturally derived materials are also known to be highly biocompatible with negligible toxicity to brain tissues. By using a safe and biocompatible coating, NPs' efficacy may be modified to improve their targeting ability to brain tissues in vivo. However, the pathological conditions of the CNS should be exploited by scientists to design well-controlled delivery nanosystems for the diagnosis and treatment of psychiatric disorders. Additionally, scientists should focus on NPs' interaction with the BBB. We assume that, in the future, our paper can help scientists plan better NP-based treatments for psychiatric disorders.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.R.S.K.; Design – A.R.S.K.; Supervision – S.S.; Resources – S.H.; Materials – M.A., F.V.; Data Collection and/or Processing – S.S., M.A., F.V.; Analysis and/or Interpretation – A.R.S.K., S.S., S.H.; Literature Search – M.A.; Writing Manuscript – S.S., S.H.; Critical Review – A.R.S.K.

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Declaration of Interests: The authors have no conflict of interest to declare.

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